Osteoporosis in adults with axial spondyloarthritis

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Submitted for the degree of Doctor of Philosophy

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2020

Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other University. It is entirely my own work. I agree that the Library may lend or copy the thesis upon request.

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Summary of Thesis

Individuals with axial spondyloarthropathy (axSpA) have increased morbidity and mortality compared to age- and sex-matched controls. A large multinational cross-sectional study (COMOSPA) described the comorbidity profile of individuals with axSpA and identified osteoporosis as the most prevalent condition. The prevalence and impact of multimorbidity has not been investigated in individuals with axSpA. Furthermore, the profile of comorbidities in individuals with axSpA in Ireland has not previously been investigated Thus, it was not known if the profile of comorbidities seen in axSpA internationally was the same in the Irish cohort. Specifically, the prevalence of osteoporosis in individuals with axSpA in Ireland was unknown. Therefore, the aim of this thesis was to examine comorbidity and multimorbidity in adults with axSpA in Ireland, with a specific focus on osteoporosis.

In pursuing this aim, four original studies, a narrative review and a systematic review with meta-analysis were completed. Study 1 was a cross-sectional analysis of the Ankylosing Spondylitis Registry of Ireland (ASRI), aiming to examine the multimorbidity profile of adults with axSpA in Ireland, with the specific objectives of (1) assessing the prevalence of multimorbidity, (2) detailing the profile of comorbidities, (3) examining the association between multimorbidity and disease outcomes, and (4) comparing the prevalence of osteoporosis in Ireland in comparison to internationally reported figures. This study identified obesity as the most prevalent comorbid condition, affecting 27% of the population. Fifty five percent of the cohort was multimorbid, defined as having at least one condition in addition to axSpA. Multimorbid individuals had more severe disease than those without multimorbidity. Less than 20% of the cohort had previously undergone dual-energy x-ray absorptiometry (DXA) assessment of their bone mineral density (BMD). However, the prevalence of osteoporosis amongst those who had undergone DXA assessment was high; at 23%, this was higher than reported in the international COMOSPA study.

The high prevalence of osteoporosis in the ASRI cohort identified the need for a comprehensive narrative review of the literature examining osteoporosis in axSpA, specifically focusing on epidemiology, assessment techniques and associations with osteoporosis and fragility fractures. Consideration of the gaps identified in the literature formed the basis of a large cross-sectional study of individuals with axSpA, with three parts.

The narrative review established the inadequacy of posteroanterior (PA) DXA in assessing BMD of the spine – our current gold standard technique. New bone formation occurs to a variable degree in the spine of individuals with axSpA and can hinder the accuracy of PA DXA, by potentially over-estimating BMD of the lumbar spine and missing existing osteoporosis. Thus,

Study 2 was designed, a cross-sectional study with the primary aim of comparing lateral and conventional DXA in their ability to examine BMD of the spine. The results of Study 2 demonstrated that lateral BMD of the lumbar spine was significantly lower than PA assessed BMD. This was the first study to demonstrate that incorporating lateral DXA into the BMD assessment of individuals with axSpA significantly increased the detection of low BMD from 35% to 58%.

Study 3 was conducted to investigate the role of biomarkers, specifically bone turnover markers (BTMs), testosterone, vitamin D and serum urate (SUA), in identifying low BMD in individuals with axSpA. Increased bone turnover was correlated with lower BMD at all sites, testosterone was inversely correlated with BMD at PA spine and higher SUA was associated with higher BMD at the spine (PA and lateral), total hip and forearm. However, the relationships were attenuated and lost statistical significance once confounding variables were introduced. Therefore, no clinically useful biomarkers to identify individuals at risk of developing osteoporosis were identified.

Study 4 aimed to explore the ability of quantitative ultrasound (QUS) of the calcaneus as a pre-screening tool to stratify individuals with axSpA according to their risk of osteoporosis. The results of this study demonstrated that QUS of the calcaneus could out-rule with 90% confidence individuals with axSpA at low risk of low BMD, negating the need for onward DXA referral in those with values above the device-specific thresholds identified in the study. This strategy had the ability to save up to 27% of DXAs in this population.

The final step in this thesis was to examine treatment options for individuals with osteoporosis in axSpA. A lack of recommendations guiding clinicians in this area represented an unmet need. The aim of the final study, Study 5, was to systematically appraise and synthesise randomised controlled trials (RCTs) and quasi(q)-RCTS examining the efficacy of pharmacological and non-pharmacological interventions on BMD in adults with axSpA. Only eight studies were eligible, with no RCTs examining non-pharmacological interventions identified. Moderate level evidence supported a conditional recommendation for the use of alendronate for low BMD of the femoral neck and IV neridronate over infliximab for low BMD of the lumbar spine. The balance of evidence did not support the use of TNFi at either spine or hip. There is a lack of high-quality RCTs guiding clinicians when treating osteoporosis in individuals with axSpA.

Acknowledgements

Firstly, I would like to thank my supervisors Dr. Barry O' Shea and Professor Fiona Wilson, for their endless support and guidance throughout this process. I am incredibly grateful for the time, energy and mentorship that they provided me with. No problem was too big, no challenge couldn't be overcome. Their dedication and encouragement have been crucial for the smooth running of the project. Thank you to Dr. Tom O' Dwyer for his experience, advice and expertise at every stage of this PhD – it would not have been possible without him. Thank you also to Professor David Kane and Professor Ronan Mullan for their enthusiastic collaboration and generosity with sharing their advice and expertise.

I am indebted to all the participants, who so willingly gave up their time to partake in this project. This project would not have been possible without you.

Thank you to Dr. Kevin McCarroll for sharing his expertise and advice for the studies. Thank you also for facilitating the collaboration with the bone clinic in St. James's Hospital. Without this seamless collaboration, this project would never have been able to get off the ground. I am very grateful to all the nursing and administrative staff of the bone clinic for their contribution.

I would like to thank all the doctors, nurses and administrative staff working in the rheumatology department in St. James's Hospital. I am proud to have been part of this fantastic department over the last three years. The academic support and personal friendships have been second to none. In particular, I would like to thank Professor Gaye Cunnane for all of her support and advice.

I wish to thank a number of people who contributed in various ways to this project:

- David Mockler of John Stearne Library for his assistance with the literature search
- Phil Gallagher for her assistance with the ASRI database
- Dr. Jason Wyse for his statistical advice
- Tochukwu Anachebe for his assistance with data collection and inputting
- Salim Sebaoui for his assistance with data inputting.

Finally, a big thank you to my family and friends for their unending love, support and guidance. Words can never express my gratitude to my amazing parents Valerie & Brendan, my brother Des, and my sister Michelle. A particular word of thanks to Michelle – her expertise in osteoporosis is what originally piqued my interest in the topic, resulting in this project. Finally, thank you to my fiancé Simon who has been by my side for every step of this PhD. This would not have been possible without his unwavering love and support.

List of Tables

Table 1-1: Amor criteria for SpA.... 4
Table 1-2: Three separate criteria for inflammatory back pain.... 11
Table 1-3: International Classification of Functioning, Disability and Health (ICF) categories included in the brief ICF core set for Ankylosing Spondylitis 22
Table 1-4: Recommended instruments for each domain of the ASAS/OMERACT core sets.... 23
Table 1-5: Calculation of the ASDAS 25
Table 2-1: Baseline characteristics of ASRI cohort.... 60
Table 2-2: Comparison of disease outcome measures between multimorbid patients and patients with axial spondyloarthropathy.... 66
Table 2-3: ANOVA investigating differences in disease outcome measures of the ASRI cohort between three groups: (1) axSpA only, (2) multimorbid with one additional chronic condition, and (3) multimorbid with two or more additional chronic conditions. 67
Table 2-4: Adjusted analyses of association between disease outcome measures (dependent variables in individual models) and presence of multimorbidity.... 68
Table 2-5: Adjusted analyses of association between disease outcome measures and severity of multimorbidity 69
Table 3-1: Summary of studies outlining the prevalence of low bone mineral density in axial spondyloarthritis. 83
Table 3-2: Summary of studies detailing factors associated with low BMD in axial spondyloarthritis 91
Table 3-3: Summary of studies outlining the prevalence of vertebral fractures in axial spondyloarthritis. 97
Table 4-1: Baseline demographic and clinical characteristics of the axSpA cohort.... 115
Table 4-2: Correlation between variables and (a) BMD site (b) difference between PA and lateral BMD. 116
Table 4-3: Difference in BMD at each measured site for a selection of variables.... 117
Table 4-4: Multiple regression model, variables associated with difference between PA and lateral BMD of the spine.... 119
Table 5-1: Baseline demographic and clinical characteristics 130
Table 5-2: Description of biomarkers, with comparison between genders.... 132
Table 5-3: Correlation between bone turnover markers and baseline characteristics, including bone mineral density, of the cohort.... 133
Table 5-4: Multivariable analysis of the effect of BTMs on FN BMD.... 139
Table 5-5: Multivariable analysis demonstrating associations between testosterone (independent variable) and measures of disease severity (dependent variables, individual models) 144

Table 5-6: Univariable and multivariable regression analysis, investigating association between testosterone and active disease 144
Table 6-1: Baseline demographic and clinical characteristics for cohort. 158
Table 6-2: Correlation matrix, demonstrating associations between quantitative ultrasound parameters and bone mineral density. 159
Table 6-3: Discriminative ability of quantitative ultrasound to diagnose low BMD 159
Table 6-4: 'Low-risk triage approach', using QUS 162
Table 6-5: 'Intermediate-risk triage approach' 163
Table 7-1: Summary of setting and design of included studies. 175
Table 7-2: Summary of participant and intervention characteristics. 180
Table 7-3: Summary of effects of interventions for each outcome, along with strength of evidence and strength/direction of recommendation. 193
Table 7-4: Summary of Recommendations 194

List of Figures

Figure 1-1: ESSG criteria for SpA 5
Figure 1-2: Non-radiographic and radiographic stages of axSpA 6
Figure 1-3: ASAS classification criteria for axial spondyloarthropathy 7
Figure 1-4: ASAS criteria for peripheral spondyloarthropathy 7
Figure 1-5: Molecular structure of HLA-B27. 15
Figure 1-6: Overview of three hypotheses outlining the role of HLA-B27 in the pathogenesis of axSpA 17
Figure 1-7: Sample mSASSS scoring 20
Figure 1-8: ASAS/OMERACT core domains for ankylosing spondylitis 21
Figure 1-9: Selected cut-offs for disease activity states using the ASDAS Score 25
Figure 1-10: Algorithm based on the ASAS/EULAR recommendations for the management of axial spondyloarthritis 28
Figure 1-11: Comorbidity and multimorbidity in rheumatic disease 35
Figure 1-12: Simplified summary of key pathways involved in osteoblast signalling during health. 44
Figure 1-13: Factors that influence the development of osteoporosis 46
Figure 1-14: Effects of antiresorptive and anabolic pharmacological treatments on bone remodelling and modelling 49
Figure 1-15: Overview of aims and objectives of thesis. 53
Figure 2-1: Current pharmacological treatment of individuals in the ASRI cohort. 61
Figure 2-2: Prevalence of comorbidities in ASRI cohort 62
Figure 2-3: Prevalence of comorbidities in the subgroup in ASRI with available DXA data 64
Figure 3-1: Simplified schematic outlining key signalling pathways in osteoblasts during inflammation 80
Figure 4-1: Summary of recruitment process of participants 114
Figure 4-2: Scatter plot demonstrating difference between BMD of the spine as measured by PA and lateral DXA, stratified by gender. 118
Figure 4-3: Prevalence of normal bone mineral density, osteopenia and osteoporosis at each measured site, in men ≥ 50 years and post-menopausal women 121
Figure 5-1: Flow of participants in biomarkers study. 131
Figure 5-2: Breakdown of BMD categories, in men ≥ 50 years and post-menopausal women, using T score. 135
Figure 5-3: Comparison of bone turnover markers, (a) CTX, (b) P1NP and (c) osteocalcin, in participants with normal and low bone mineral density measured at the femoral neck. 136
Figure 5-4: Prevalence of low BMD in men < 50 years and pre-menopausal women 141

Figure 6-1: Demonstration of use of GE Lunar Achilles InSight densitometer. 154
Figure 6-2: Flow-chart of participants eligible for analysis. 157
Figure 6-3: ROC curves for each QUS parameter (BUA, SOS, SI, T score) as screening tools for detecting low BMD at (a) PA lumbar spine, (b) lateral spine, (c) femoral neck, (d) total hip, and (e) any site. 160
Figure 7-1: PRISMA flow diagram outlining the study selection process. 173
Figure 7-2: Risk of bias by study 185
Figure 7-3: Risk of bias by domain. 185
Figure 7-4: Forest plots demonstrating effect of alendronate on outcomes (lumbar spine, femoral neck, total hip, intertrochanteric hip). 188
Figure 7-5: Forest plots demonstrating effect of alendronate in combination with steroids on outcomes (lumbar spine, femoral neck). 188
Figure 7-6: Forest plot demonstrating effect of TNFi on BMD (lumbar spine, femoral neck and total hip). 190
Figure 7-7: Forest plot demonstrating results of sensitivity analysis testing effect of TNFi on BMD (lumbar spine and femoral neck). 190
Figure 7-8: Forest plot demonstrating effect of neridronate compared to infliximab on BMD (lumbar spine, femoral neck and total hip). 191

List of Appendices

A	Publications from thesis	264
B	Protocols	357
C	Research ethics approval	370
D	Outcome measures	374
E	Patient information leaflets & consent	383
F	Search strategy	395

Academic output from thesis

Published manuscripts

- Fitzgerald G, Gallagher P, O' Shea FD. (2020) Multimorbidity is common in axial spondyloarthropathy and is associated with worse disease outcomes: results from the Ankylosing Spondylitis Registry of Ireland cohort. *Journal of Rheumatology*. Feb;47(2):218-226. Epub 2019 May 15.

- Fitzgerald GE, Anachebe T, McCarroll KG, O'Shea FD. (2020) Calcaneal quantitative ultrasound has a role in out ruling low bone mineral density in axial spondyloarthropathy. *Clinical Rheumatology*. Jan 17. doi: 10.1007/s10067-019-04876-9. [Epub ahead of print].

- Fitzgerald G, Anachebe T, McCarroll K, O' Shea F. (2020) Measuring bone density in axial SpA: time to turn things on their side? *International Journal of Rheumatic Diseases*. Jan 7. doi: 10.1111/1756-185X.13765. [Epub ahead of print].

- Fitzgerald G, O' Shea F. (2017) The fascinating paradox of osteoporosis in axial spondyloarthropathy. *Journal of Rheumatology*. 44(12):1767-76.

Published conference abstracts

- Fitzgerald G, Wyse J, Anachebe T, Mullan R, Kane D, McCarroll K, O' Shea F. (2018) Lateral DXA More Effective in Detecting Osteoporosis Than Conventional DXA in Axial Spondyloarthropathy [abstract]. *Arthritis and Rheumatology*; 70 (suppl 10). https://acrabstracts.org/abstract/lateral-dxa-more-effective-in-detecting-osteoporosis-than-conventional-dxa-in-axial-spondyloarthropathy/. Accessed November 27, 2018.

- Fitzgerald G, Anachebe T, Mullan R, Kane D, McCarroll K, O' Shea F. (2018) Quantitative Ultrasound of the Calcaneus Has a Role to Play in Detecting Low Bone Mineral Density in Axial Spondyloarthropathy Patients [abstract]. *Arthritis and Rheumatology*.; 70 (suppl 10). https://acrabstracts.org/abstract/quantitative-ultrasound-of-the-calcaneus-has-a-role-to-play-in-detecting-low-bone-mineral-density-in-axial-spondyloarthropathy-patients/. Accessed November 27, 2018.

- Fitzgerald G, Anachebe T, Mullan R, Kane D, McCarroll K, O' Shea F. (2018) Higher Serum Uric Acid Levels Protect Against Osteoporosis in Patients with Axial Spondyloarthropathy [abstract]. *Arthritis and Rheumatology*. 2018; 70 (suppl 10). https://acrabstracts.org/abstract/higher-serum-uric-acid-levels-protect-against-osteoporosis-in-patients-with-axial-spondyloarthropathy/. Accessed November 27, 2018.

- Fitzgerald GE, Anachebe T, McCarroll K, O' Shea F. (2018) Syndesmophytes prevent accurate DXA assessment of the spine in axial spondyloarthropathy [abstract]; *Clinical and Experimental Rheumatology*;36:742.

- Fitzgerald GE, Anachebe T, McCarroll K, O' Shea F. (2018) Osteoporosis commonly occurs in axial spondyloarthropathy [abstract]. *Clinical and Experimental Rheumatology*;36:742.

- Fitzgerald G, Anachebe T, O' Shea F. (2018) FRI0196 Traditional dxa underestimates bone mineral density of the spine in axial spondyloarthropathy [abstract]. *Annals of the Rheumatic Diseases*;77:639. http://dx.doi.org/10.1136/annrheumdis-2018-eular.6296

- Fitzgerald G, Anachebe T, Mullan R, Kane D, McCarroll K, O' Shea F. (2018) Quantitative Ultrasound of the Calcaneus Has a Role to Play in Detecting Low Bone Mineral Density in Axial Spondyloarthropathy Patients [abstract]. *Arthritis and Rheumatol*ogy; 70 (suppl 10). https://acrabstracts.org/abstract/quantitative-ultrasound-of-the-calcaneus-has-a-role-to-play-in-detecting-low-bone-mineral-density-in-axial-spondyloarthropathy-patients/. Accessed November 27, 2018.

- Fitzgerald G, Anachebe T, O' Shea F. (2018) THU0255 Low bone mineral density is common in axial spondyloarthropathy [abstract]. *Annals of the Rheumatic Diseases*;77:347. http://dx.doi.org/10.1136/annrheumdis-2018-eular.6287.

Academic accolades

- **William-Stokes Award, Royal College of Physicians of Ireland (2018)**: awarded for research entitled "Lateral DXA performs better than conventional DXA in detecting osteoporosis in axial spondyloarthropathy".

- **American College of Rheumatology Annual Meeting Poster Tour, Chicago (2018):** abstract entitled "Higher serum uric acid levels protect against osteoporosis in patients with axial spondyloarthropathy" chosen to be part of the poster tour.

- **ESCEO-Eli Lilly Scholarship, WCO-IOF-ESCEO, Krakow (2018)**: awarded for research on "Low bone mineral density is common in Axial Spondyloarthropathy".

Abbreviations

ß$_2$m	ß2-microglobulin
AAU	Acute anterior uveitis
ACPA	Antibodies to citrullinated protein
ACR	American College of Rheumatology
ALP	Alkaline phosphatase
ANOVA	Analysis of variance
AS	Ankylosing Spondylitis
ASAS	Assessment of SpondyloArthritis Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
ASRI	Ankylosing Spondylitis Registry of Ireland
AUC	Area under the curve
AxSpA	Axial spondyloarthropathy
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
bDMARD	Biological Disease-modifying antirheumatic drug
B-ICF-CS	Brief International Classification of Functioning, Disability and Health Core Sets
BMD	Bone mineral density
BMI	Body mass index
BMO	Bone marrow oedema
BMP	Bone morphogenetic protein
BTM	Bone turnover markers
BUA	Broadband ultrasound attenuation
CI	Confidence interval
C-ICF-CS	Comprehensive International Classification of Functioning, Disability and Health Core Sets
COMOSPA	Comorbidities in Spondyloarthropathy study
csDMARD	Conventional synthetic disease modifying anti-rheumatic drug
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	Computed tomography
CTX	C-terminal telopeptides of type 1 collagen
CV	Cardiovascular

DC-ART	Disease-controlling antirheumatic treatments
DISH	Diffuse idiopathic skeletal hyperostosis
DKK	Dickkopf-related protein
DMARD	Disease-modifying antirheumatic drug
DNA	Deoxyribonucleic acid
DXA	Dual-energy x-ray absorptiometry
EAM	Extra-articular manifestations
EnA	Enteropathic arthropathy
ER	Endoplasmic reticulum
ERAP	Endoplasmic reticulum aminopeptidase
ESR	Erythrocyte sedimentation rate
ESSG	European Spondyloarthropathy Study Group
EU	European Union
EULAR	European League Against Rheumatism
FDA	Federal Drugs Agency
GDP	Gross domestic product
GE	General Healthcare company
GP	General Practitioner
GPRD	General practice research database
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GWAS	Genome-wide association studies
HAQ	Health Assessment Questionnaire
HLA	Human leucocyte antigen
HRpQCT	High-resolution peripheral quantitative computed tomography
HSD	Honestly significant difference
HTN	Hypertension
IBD	Inflammatory bowel disease
IBP	Inflammatory back pain
ICF	International Classification of Functioning, Disability and Health
IHD	Ischaemic heart disease
IL	Interleukin
ISCD	International Society of Clinical Densitometry
JIA	Juvenile idiopathic arthritis
LBP	Low back pain
LR	Likelihood ratio
LRP	Lipoprotein receptor-related proteins
LSC	Least significant change

MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCII	Minimum clinically important improvement
M-CSF	Macrophage colony-stimulating factor
MCU	Multicellular unit
MD	Mean difference
MHC	Major histocompatibility complex
MiRNA	Micro ribonucleic acid
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
MSD	Musculoskeletal disease
mNY	Modified New York
mSASSS	Modified Stoke Ankylosing Spondylitis Spinal Score
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NK	Natural killer
NPV	Negative predictive value
nr-AxSpA	Non-radiographic axial spondyloarthropathy
NR	Not reported
NRS	Numerical rating score
NS	Not significant
NSAID	Non-steroidal anti-inflammatory drug
OASIS	Outcome in ankylosing spondylitis international study
OMERACT	Outcome Measures in Rheumatology Clinical Trials
OPG	Osteoprotegerin
OR	Odds ratio
P1NP	N-propeptide of type 1 collagen
PA	Posterior-anterior
PF	Proximal femur
PPV	Positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PRO	Patient reported outcomes
PsA	Psoriatic arthritis
PsO	Psoriasis
PTH	Parathyroid hormone
PUD	Peptic ulcer disease
QALY	Quality adjusted life years
qCT	Quantitative computed tomography

qRCT	Quasi randomised controlled trial
QUS	Quantitative ultrasound
RA	Rheumatoid arthritis
RANK	Receptor activator of nuclear factor-κß
RANKL	Receptor activator of nuclear factor-κß ligand
RCT	Randomised controlled trial
ReA	Reactive arthritis
REC	Research ethics committee
RoB	Risk of bias
ROC	Receiver operating characteristics
RUNX	Runt-related transcription factor
SD	Standard deviation
SEQCT	Single energy quantitative computed tomography
SI	Stiffness index
SIJ	Sacroiliac joints
SM-ARD	Symptom-modifying anti-rheumatic drugs
SMD	Standardised mean difference
SNP	Single-nucleotide polymorphisms
SOE	Strength of evidence
SOR	Strength of recommendation
SOS	Speed of sound
SOST	Sclerostin
SpA	Spondyloarthropathy
SPA	Single-photon absorptiometry
SPACE	SPondyloarthritis Caught Early cohort
SSc	Systemic sclerosis
SSZ	Sulphasalazine
STIR	Short tau inversion recovery
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SUA	Serum urate
TB	Tuberculosis
TBS	Trabecular bone score
TGF	Transforming growth factor
TH	Total hip
Th17	T-helper cell 17
TNFi	Tumour necrosis factor inhibitor
UK	United Kingdom

USA	United States of America
uSpA	Undifferentiated spondyloarthropathy
VAS	Visual analogue scale
vBMD	Volumetric bone mineral density
VF	Vertebral fractures
VFA	Vertebral fracture assessment
WB	Whole body
WHO	World Health Organisation

Table of contents

CHAPTER 1 INTRODUCTION 1

1.1 SPONDYLOARTHROPATHY 1
1.2 HISTORICAL ASPECTS 1
1.3 CLASSIFICATION CRITERIA 2
1.3.1 Modified New York criteria 3
1.3.2 Amor criteria and European Spondyloarthropathy Study Group (ESSG) criteria for spondyloarthropathy 3
1.3.3 Assessment of SpondyloArthritis Society (ASAS) criteria 5
1.4 EPIDEMIOLOGY OF AXIAL SPONDYLOARTHROPATHY 8
1.4.1 Age of presentation 8
1.4.2 Prevalence 8
1.4.3 Gender differences 9
1.5 CLINICAL PRESENTATION 9
1.5.1 Back pain 9
1.5.2 Peripheral disease 11
1.5.3 Extra-articular manifestations (EAM) 12
1.6 PATHOGENESIS 13
1.6.1 HLA-B27 13
1.6.2 Other genetics of AS 17
1.7 IMAGING IN AXSPA 18
1.7.1 X-ray of SI joints in axSpA 18
1.7.2 MRI of SI joints 18
1.7.3 Imaging of spine 19
1.7.4 Other imaging modalities 19
1.8 DIAGNOSTIC PITFALLS 20
1.9 OUTCOME ASSESSMENT 21
1.9.1 Overview of instruments to assess disease outcomes 24
1.10 MANAGEMENT OF AXSPA 27
1.10.1 Non-steroidal anti-inflammatory drugs (NSAIDs) 30
1.10.2 Tumour necrosis factor-inhibitors (TNFi) 30
1.10.3 Interleukin-17 inhibition 31
1.11 OUTCOMES IN AXSPA 31
1.11.1 Mortality in axSpA 31
1.11.2 Morbidity in axSpA 32
1.12 AGEING POPULATIONS 33
1.12.1 Epidemiology and demographics 33
1.12.2 Challenges with ageing populations 33
1.12.3 Multimorbidity 34

1.12.4 Multimorbidity in rheumatic diseases *36*
1.13 OSTEOPOROSIS 37
1.14 RELEVANT DEFINITIONS 37
1.14.1 World Health Organisation definition *37*
1.14.2 International Society of Clinical Densitometry definition *37*
1.14.3 Osteoporotic fracture definition *37*
1.15 ASSESSMENT OF BMD 38
1.15.1 Dual-energy x-ray absorptiometry (DXA) *38*
1.15.2 Quantitative computed tomography (qCT) *38*
1.15.3 Trabecular bone score (TBS) *39*
1.16 EPIDEMIOLOGY OF OSTEOPOROSIS 39
1.16.1 Global prevalence *39*
1.16.2 Economic burden *40*
1.16.3 Fracture sites *40*
1.17 NORMAL BONE PHYSIOLOGY 41
1.18 PATHOPHYSIOLOGY OF OSTEOPOROSIS 45
1.18.1 Bone turnover markers *46*
1.18.2 Vitamin D *47*
1.19 MANAGEMENT OF OSTEOPOROSIS 48
1.19.1 Lifestyle measures *48*
1.19.2 Bisphosphonates *48*
1.19.3 RANK ligand inhibitor *49*
1.19.4 Teriparatide *49*
1.19.5 Other pharmacological treatments *50*
1.20 THESIS AIMS AND OBJECTIVES 51

CHAPTER 2 CROSS-SECTIONAL ANALYSIS OF COMORBIDITIES IN AXIAL SPONDYLOARTHROPATHY: RESULTS FROM THE ANKYLOSING SPONDYLITIS REGISTRY OF IRELAND (ASRI) 54

2.1 INTRODUCTION 54
2.2 METHODS 55
2.2.1 Ankylosing Spondylitis Registry of Ireland (ASRI) *55*
2.2.2 Outcome measures *57*
2.2.3 Multimorbidity *58*
2.2.4 Statistical analysis *58*
2.3 RESULTS 59
2.3.1 Baseline characteristics of ASRI cohort *59*
2.3.2 Co-morbidity profile of ASRI cohort *59*
2.3.3 Multimorbidity in axSpA *65*
2.3.4 Regression analysis *67*

2.4 DISCUSSION 70
2.4.1 Summary of findings 70
2.4.2 Comparison of our findings with existing literature 70
2.4.3 Limitations 73
2.4.4 Strengths 74
2.4.5 Future directions 74
2.5 CONCLUSIONS 75

CHAPTER 3 THE PARADOX OF OSTEOPOROSIS IN AXIAL SPONDYLOARTHROPATHY 76

3.1 INTRODUCTION 76
3.2 OSTEOPOROSIS IN CHRONIC INFLAMMATORY DISEASE 76
3.3 BONE REMODELLING IN INFLAMMATORY DISEASE 77
3.4 PATHOLOGICAL BONE REMODELLING IN AXSPA 78
3.5 EPIDEMIOLOGY OF OSTEOPOROSIS IN AXSPA 81
3.6 FACTORS ASSOCIATED WITH OSTEOPOROSIS IN AXSPA 88
3.6.1 Gender 88
3.6.2 Disease duration 88
3.6.3 Disease severity 89
3.6.4 Other risk factors 90
3.7 SYSTEMIC OR LOCAL PROCESS 90
3.8 FRACTURES IN AXSPA 95
3.9 DIFFICULTIES WITH ASSESSING BMD IN AXSPA 100
3.10 EULAR GUIDELINES 102
3.11 BIOMARKERS 102
3.11.1 Bone turnover markers 102
3.11.2 Vitamin D 104
3.11.3 Testosterone 104
3.11.4 Serum urate (SUA) 105
3.12 FUTURE RESEARCH AREAS 105
3.13 CONCLUSION 106

CHAPTER 4 MEASURING BONE DENSITY IN AXIAL SPONDYLOARTHROPATHY: TIME TO TURN THINGS ON THEIR SIDE? 107

4.1 BACKGROUND 107
4.2 AIMS 108
4.3 METHODS 109
4.3.1 Study design & setting 109
4.3.2 Population 109

4.3.3 Demographic and disease-related data ... *109*
4.3.4 Outcome measures ... *110*
4.3.5 Bone mineral density ... *111*
4.3.6 Bias ... *112*
4.3.7 Statistical methods ... *112*
4.4 RESULTS ... 113
4.4.1 Baseline characteristics ... *113*
4.4.2 Measured BMD of spine (PA and lateral projections of DXA) and hip ... *113*
4.4.3 Comparison of lumbar spine BMD using PA and lateral DXA ... *114*
4.4.4 Prediction of difference between PA and lateral BMD ... *119*
4.4.5 Prevalence of low BMD according to WHO criteria ... *119*
4.4.6 Associations with low BMD ... *120*
4.4.7 Associations with osteoporosis ... *122*
4.4.8 Fractures ... *122*
4.5 DISCUSSION ... 123
4.5.1 Limitations ... *126*
4.6 CONCLUSION ... 126

CHAPTER 5 BIOMARKERS IN AXSPA: BONE TURNOVER MARKERS, SERUM URATE, VITAMIN D, TESTOSTERONE ... 127

5.1 INTRODUCTION ... 127
5.2 AIMS ... 128
5.3 METHODS ... 128
5.3.1 Study design, setting & population ... *128*
5.3.2 Data collection ... *128*
5.3.3 Statistical analysis ... *129*
5.4 RESULTS ... 129
5.4.1 Baseline characteristics of the participants ... *129*
5.4.2 Bone turnover markers ... *131*
5.4.3 BTMs and osteoproliferation ... *139*
5.4.4 Vitamin D ... *142*
5.4.5 Testosterone ... *142*
5.4.6 Serum Urate (SUA) ... *145*
5.5 DISCUSSION ... 145
5.5.1 Summary of findings: biomarkers and osteoporosis ... *145*
5.5.2 Relationship between osteoporosis and osteoproliferation ... *148*
5.5.3 Biomarkers and disease activity ... *149*
5.5.4 Limitations ... *150*
5.6 CONCLUSION ... 150

CHAPTER 6 QUANTITATIVE ULTRASOUND OF THE HEEL – SUITABLE FOR TRIAGE? 151

6.1 INTRODUCTION 151
6.2 AIMS 153
6.3 METHODS 153
6.3.1 Study design, setting & population 153
6.3.2 Data collection 154
6.3.3 Thresholds for QUS measurements 155
6.3.4 Statistical analysis 155
6.4 RESULTS 156
6.4.1 Participant characteristics 156
6.4.2 Correlation analysis between QUS parameters and BMD 157
6.4.3 ROC curve analysis: discriminant ability of each QUS parameter to detect low BMD and osteoporosis 157
6.4.4 Cut-off values for 'low-risk triage approach' 161
6.4.5 Cut-off values for 'high-risk triage approach' 161
6.4.6 Cut-off values for 'intermediate-risk triage approach' 161
6.5 DISCUSSION 164
6.5.1 Limitations 167
6.6 CONCLUSION 167

CHAPTER 7 INTERVENTIONS, PHARMACOLOGICAL AND NON-PHARMACOLOGICAL FOR MANAGING BONE HEALTH IN AXIAL SPONDYLOARTHROPATHY: SYSTEMATIC REVIEW AND META-ANALYSIS, WITH RECOMMENDATIONS 168

7.1 INTRODUCTION 168
7.2 AIMS 168
7.2.1 Specific objectives 169
7.3 METHODS 169
7.3.1 Protocol and registration 169
7.3.2 Study eligibility criteria 169
7.3.3 Search methods for identification of studies 170
7.3.4 Assessment of risk of bias in included studies 171
7.3.5 Quality of evidence 171
7.3.6 Measures of treatment effect 171
7.3.7 Data synthesis 172
7.4 RESULTS 172
7.4.1 Study selection 172
7.4.2 Study characteristics 173

7.4.3 Intervention *178*
7.4.4 Risk of bias in included studies *183*
7.4.5 Effects of interventions *186*
7.5 DISCUSSION 195
7.5.1 Summary of main results *195*
7.5.2 Comparison with existing reviews *197*
7.5.3 Clinical implications *198*
7.5.4 Limitations *198*
7.5.5 Future research *199*
7.6 CONCLUSION 199

CHAPTER 8 DISCUSSION 201

8.1 INTRODUCTION 201
8.2 SUMMARY OF MAIN FINDINGS 201
8.3 CLINICAL IMPLICATIONS 204
8.3.1 Comorbidities: a profile of individuals with axSpA *204*
8.3.2 Multimorbidity in axSpA: a real concern *205*
8.3.3 Osteoporosis in axSpA: when should we screen? *206*
8.3.4 Osteoporosis in axSpA: how should we screen? *207*
8.3.5 Vertebral fractures in axSpA: osteoporosis or osteoproliferation? *207*
8.3.6 Osteoporosis in axSpA: can we use biomarkers for diagnosis? *208*
8.3.7 The role of testosterone in disease activity *208*
8.3.8 Osteoporosis in axSpA: can we triage individuals? *209*
8.3.9 Osteoporosis in axSpA: how do we treat? *209*
8.4 LIMITATIONS OF THE THESIS 210
8.5 FUTURE RESEARCH DIRECTIONS 211

CHAPTER 9 CONCLUSION 215

CHAPTER 10 REFERENCES 217

Chapter 1 Introduction

1.1 Spondyloarthropathy

'Seronegative spondyloarthritides' was the original term proposed by Moll et al in 1974 to describe a group of inter-related disorders now known as spondyloarthropathy (SpA) (Moll et al., 1974): psoriatic arthritis (PsA), reactive arthritis (ReA), arthritis associated with inflammatory bowel disease (IBD), a subgroup of juvenile idiopathic arthritis (JIA) and ankylosing spondylitis (AS) (Moll et al., 1974). This was based on the recognition that there were a group of disorders with similar clinical characteristics no matter the diagnosis, along with a clustering of these disorders amongst families and even within the same individual. The association of these conditions with human leucocyte antigen-B27 (HLA-B27) was found following animal work, where HLA-B27 transgenic mice were noted to develop clinical features seen in humans with SpA (Hammer et al., 1990).

1.2 Historical aspects

Ankylosing Spondylitis (AS) is the prototype SpA condition. It has a number of eponyms, including Bechterew's disease and Marie-Strumpell's disease (Spencer et al., 1980). Changes of AS in skeletal remains have been seen as far back as the Egyptian era (Spencer et al., 1980), although it is likely that some of the skeletal changes reported as AS were more degenerative in nature. The first family study of AS was of the Medicis, a famous Florentine family, and took place when their bodies were removed from the Medici chapel in 1945. Four male members of this family, spanning the years 1389 to 1516, almost certainly had AS (Spencer et al., 1980). Irish physician Bernard Connor, a Co. Kerry native who obtained his medical degree in France, gave the first clear description of AS in 1691, which was based on a skeleton with the disease: "all the bones [..] united to make but one bone without articulation" (Blumberg, 1958).

Following World War 2, interest in AS increased, as it was recognised that the prevalence was relatively high, both during the war and the conscription to armed forces that occurred afterwards; this increased interest led to the hereditary nature of AS being discovered (Hart, 1948). There was an early belief in the United States of America (USA) that AS represented a variation of rheumatoid arthritis (RA) (Boland, 1961). However, in Europe, the opinion was that AS

represented a disease entity independent to RA, a belief subsequently confirmed with the discovery of rheumatoid factor (Spencer et al., 1980).
In 1960, the first attempt at classification criteria was made, following meetings at the National Institutes of Health (NIH), Maryland, USA, and in Rome; these were subsequently amended at a third symposium in New York, culminating in the 'New York criteria' (Spencer et al., 1980). Since then, multiple different classification criteria have been introduced.

1.3 Classification criteria

The purpose of classification criteria is to provide a standardised definition of a condition, with the primary intention of creating well-defined homogeneous cohorts of affected individuals, which will allow clinical research to be performed (Aggarwal et al., 2015). Therefore, they are not intended to capture **all** possible manifestations of a disease, but rather the majority. This allows interpretation of findings and comparison between studies with the same populations (Aggarwal et al., 2015). By their nature, classification criteria are designed to be highly specific, in order to limit the number of people without the disease who are wrongly classified as positive i.e. false positives. The draw-back of classification criteria is that with a clear 'yes' or 'no' result, there will invariably be individuals with the disease who do not fulfil the classification criteria (Braun et al., 2015). Therefore, classification criteria can limit the extrapolation of the results of studies to real-life individuals with the diagnosis, as affected individuals may not share all aspects of the disease.

In contrast, diagnostic criteria are intended to be used to guide the care of individual patients (Aggarwal et al., 2015, Braun et al., 2015). They provide clinicians with signs, symptoms and diagnostic tests that can be used in a clinical setting. In order to capture all patents with the disease, they must be sufficiently broad, reflecting the variations that can present with all diseases. They are also more flexible, as they take negative findings and the expert's opinion into consideration (Braun et al., 2015). Rheumatology is faced with unique challenges in that many rheumatic conditions share features with other non-rheumatic conditions. Therefore, diagnostic criteria can be challenging to develop and as a result there are very few validated diagnostic criteria in rheumatology. Due to the difficulties associated with validating diagnostic criteria, the American College of Rheumatology (ACR) no longer funds or endorses diagnostic criteria (Aggarwal et al., 2015). More commonly, a physician's clinical acumen is employed to establish a diagnosis based on the interpretation of combinations of signs, symptoms, available diagnostic results and knowledge of the prevalence and epidemiology of conditions (Aggarwal et al., 2015).

However, in reality diagnostic and classification criteria represent opposite ends of a continuum (Yazici, 2009).

1.3.1 Modified New York criteria

The original criteria for the diagnosis of AS were referred to as the modified New York (mNY) criteria, published in 1984 (van der Linden et al., 1984). To fulfil these criteria, individuals were required to have bilateral grade 2-4 OR unilateral grade 3-4 sacroiliitis on plain x-rays, in addition to at least one of the following clinical criteria:

- Inflammatory back pain, defined as low back pain lasting ≥ 3 months, improved by exercise and not relieved by rest
- Limitation of lumbar spine in sagittal and frontal planes
- Limitation of chest expansion (relative to normal values corrected for age and sex).

Although these criteria are specific, they do not allow individuals with clinical features of AS and sacroiliitis on magnetic resonance imaging (MRI) imaging, but without plain film changes, to receive a diagnosis of AS.

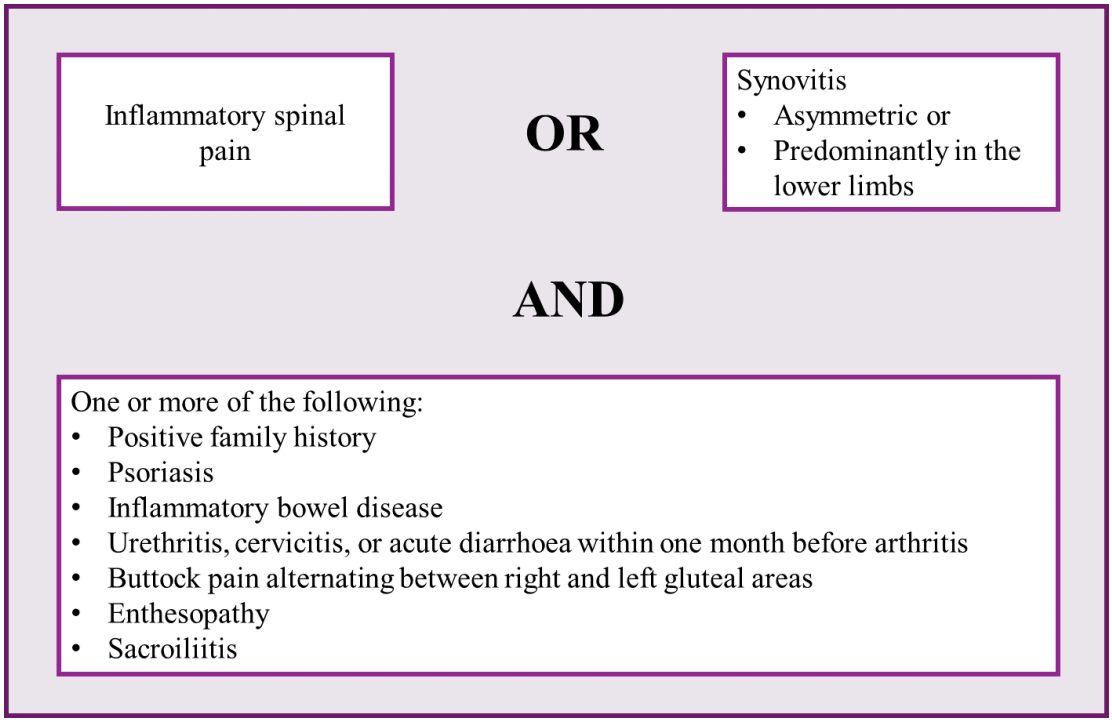
1.3.2 Amor criteria and European Spondyloarthropathy Study Group (ESSG) criteria for spondyloarthropathy

In 1990, Amor et al (Amor et al., 1990) published a set of classification criteria for the group of spondyloarthropathies (Table 1-1). A year later, the European Spondyloarthropathy Study Group (ESSG) published different criteria for the classification of SpA (see Figure 1-1) (Dougados et al., 1991). Both of these criteria aimed to cater for a wider spectrum of SpA, including individuals who had early disease but no x-ray changes, who were classified as undifferentiated SpA (uSpA).

Table 1-1: Amor criteria for SpA (Amor et al., 1990).

Criterion	Points
Clinical symptoms or past history:	
• Lumbar or dorsal pain during the night, or morning stiffness of lumbar or dorsal spine	1
• Asymmetric oligoarthritis	2
• Buttock pain	1
- if affecting alternately the right or left buttock	2
• Sausage-like toe or digit	2
• Heel pain or any other well defined enthesiopathy	2
• Iritis	2
• Non-gonococcal urethritis or cervicitis accompanying, or within one month before, onset of arthritis	1
• Acute diarrhoea accompanying, or within 1 month before, the onset of arthritis	1
• Presence or history of psoriasis, balanitis, or inflammatory bowel disease (Ulcerative Colitis or Crohn disease)	2
Radiological finding:	
• Sacroiliitis (grade ≥2 if bilateral; grade ≥3 if unilateral)	3
Genetic background:	
• Presence of HLA-B27, or familial history of ankylosing spondylitis, Reiter syndrome, uveitis, psoriasis, or chronic entercolopathies	2
Response to treatment:	
• Good response to NSAIDs in less than 48h, or relapse of the pain in less than 48h if NSAIDs discontinued	2
An individual is considered to have spondyloarthritis if the sum of the point counts is 6 or more. A total point count of five or more classifies for probable spondyloarthritis	
HLA: human leucocyte antigen; NSAID: non-steroidal anti-inflammatory drugs.	

Figure 1-1: European Spondyloarthropathy Study Group (ESSG) criteria for SpA (Dougados et al., 1991).



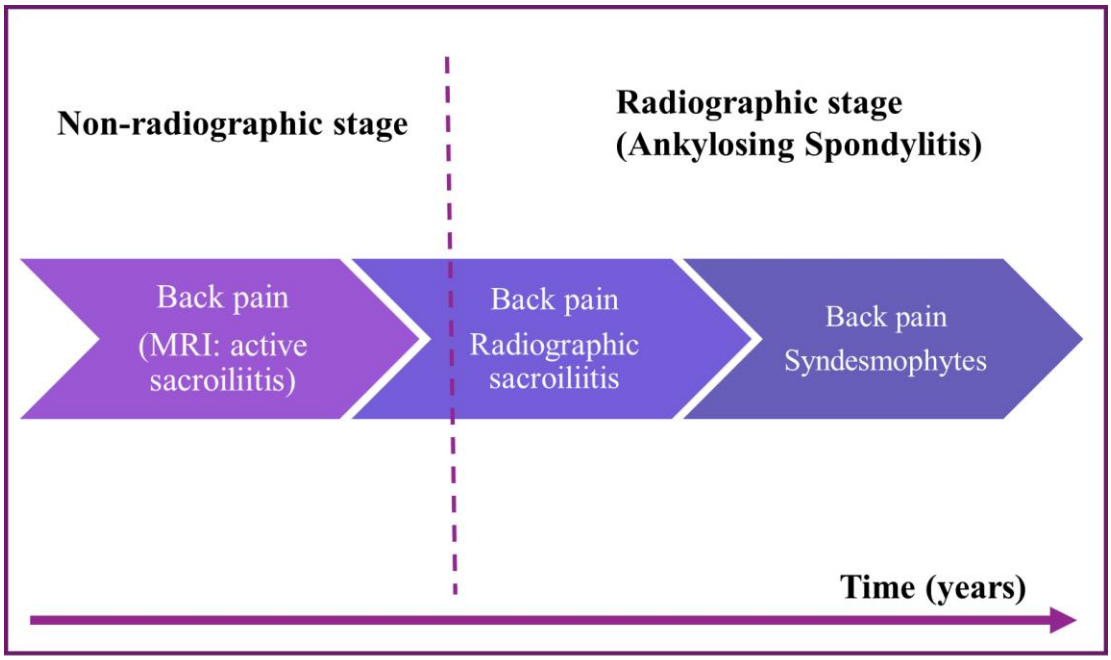
1.3.3 Assessment of SpondyloArthritis Society (ASAS) criteria

Although the ESSG criteria were an improvement upon the mNY criteria, it was increasingly recognised that in many adults with AS, radiographic sacroiliitis could take many years to develop from the onset of inflammatory back pain. In one ten-year follow-up study of people with symptoms suggestive of early AS but without x-ray changes, the prevalence of radiographic sacroiliitis increased to 36% at five years and 59% at ten years (Mau et al., 1988).

The introduction of MRI imaging to the assessment of AS confirmed that individuals with IBP symptoms but without x-ray changes were indeed experiencing inflammation in the sacroiliac joints and/or spine (Oostveen et al., 1999). Further to that, it was recognised that the presence or absence of radiographic sacroiliitis did not primarily dictate burden of disease and quality of life (Rudwaleit et al., 2005). Thus, it was concluded that the presence and absence of radiographic sacroiliitis actually represented a continuum of a single disease, rather than two separate disease entities, and that individuals with predominantly axial symptoms should be regarded as the same disease entity as AS individuals (Rudwaleit et al., 2005). The term 'non-radiographic axial SpA' (nr-axSpA) was proposed to refer to individuals without definite sacroiliitis on plain films (Rudwaleit et al., 2009a) (see Figure 1-2).

It was recognised that individuals with nr-axSpA responded to treatment as well as those with AS, therefore it was important to be able to recognise early AS, or nr-axSpA (Callhoff et al., 2015).

Figure 1-2: Non-radiographic and radiographic stages of axSpA. The vertical line indicates the differentiation between non-radiographic axSpA and radiographic SpA (AS) (Rudwaleit et al., 2005).



This precipitated a further change in classification criteria (Rudwaleit et al., 2009b) and in 2009, the Assessment of SpondyloArthritis Society (ASAS) criteria for axSpA were published (see Figure 1-3), with an 'imaging arm' and 'clinical arm'. Subsequently, the ASAS classification criteria for peripheral spondyloarthritis were published in 2011 (see Figure 1-4) (Rudwaleit et al., 2011).

Figure 1-3: Assessment of SpondyloArthritis Society (ASAS) classification criteria for axial spondyloarthropathy (Rudwaleit et al., 2009c).

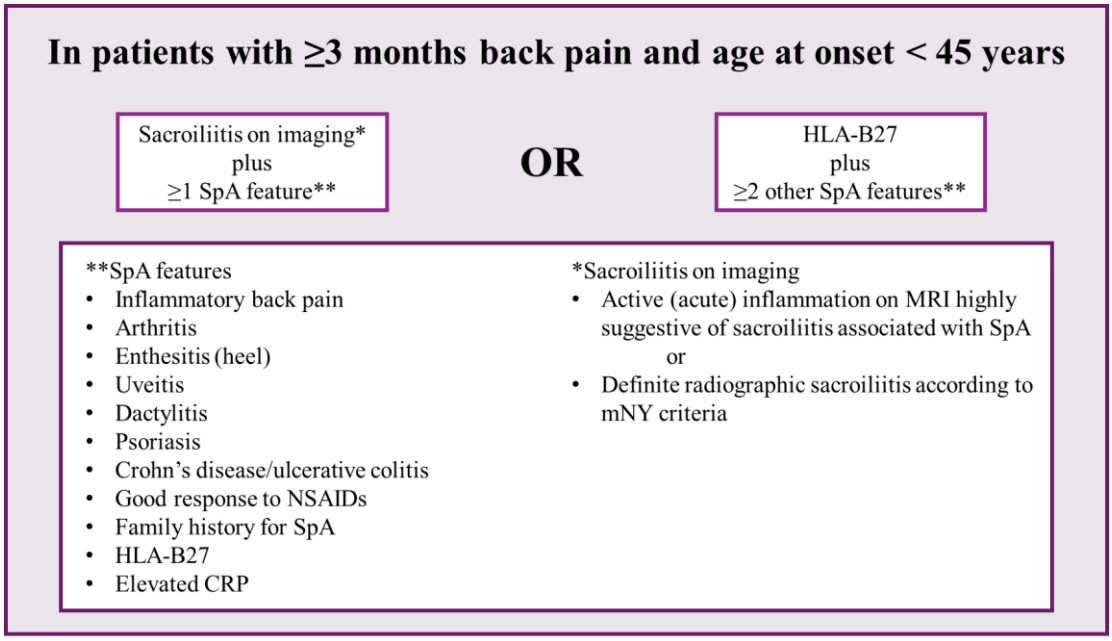
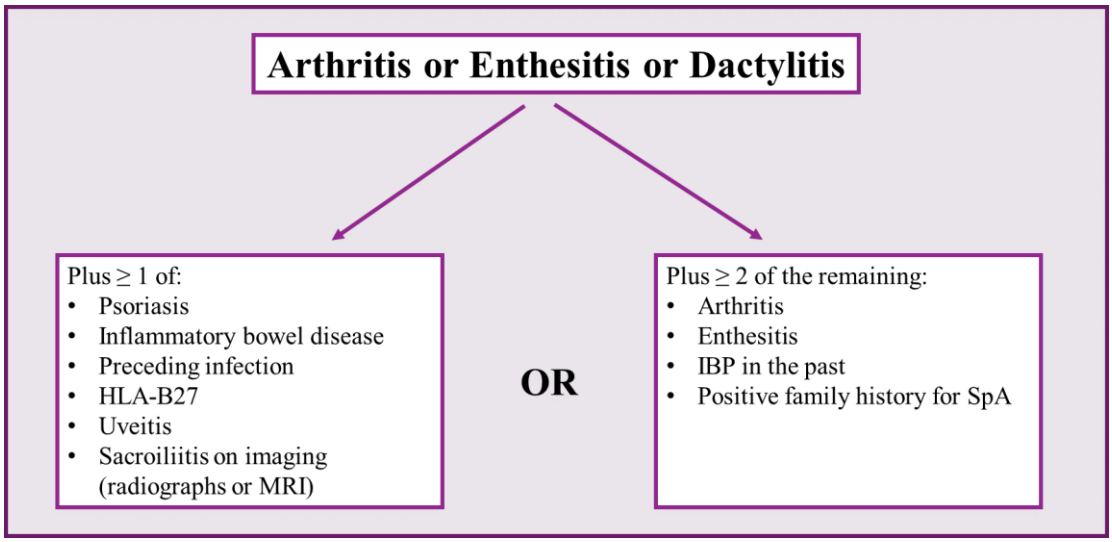


Figure 1-4: ASAS criteria for peripheral spondyloarthropathy (Rudwaleit et al., 2011).



1.4 Epidemiology of axial spondyloarthropathy

1.4.1 Age of presentation

Axial spondyloarthropathy (axSpA) typically presents in the third decade of the life, and almost exclusively before the age of 45 years (Olivieri et al., 2013). It is associated with a significant delay in diagnosis, estimated at an average of seven years in a meta-analysis of 23,883 individuals (Jovani et al., 2017). However, axSpA presents earlier in individuals who are HLA-B27 positive, by about five years (Sieper and Poddubnyy, 2017, Akkoc et al., 2017).

1.4.2 Prevalence

Prior to the introduction of the ASAS criteria, SpA was estimated globally to have a prevalence of approximately 1% (Akkoc, 2008, Reveille et al., 2012). The prevalence of AS varies widely amongst populations, which can be at least partly explained by differences in background HLA-B27 prevalence (van Tubergen, 2014). The prevalence of HLA-B27 in Europe varies from 2-25% (Khan, 1995), with the highest in Scandinavian countries (Norway, Sweden, Finland) (Gran et al., 1984, Johnsen et al., 1992). In contrast HLA-B27 is exceedingly rare in Japan and Arab countries (Mustafa et al., 2012, Hukuda et al., 2001), and almost non-existent in some populations such as indigenous tribes of South America (Khan, 1995). Papua New Guinea, on the other hand, has the highest prevalence in the Pawaia tribe, where 53% of people are affected (Bhatia et al., 1988).

In 2016, Stolwijk et al systematically summarised the global prevalence of SpA and its subtypes, reporting a worldwide prevalence of 0.55% (0.37 to 0.77), with the lowest prevalence in South-East Asia (pooled prevalence 0.20%, 95% CI 0.00 to 0.66) and the highest in the Northern Arctic communities (pooled prevalence 1.61%, 95% CI 1.27 to 2.00) (Stolwijk et al., 2016). The prevalence of SpA in Europe was 0.54% (95% CI 0.36 to 0.78) and North America 1.35% (95% CI 0.44 to 2.79). In that review, the prevalence of axSpA was based on point estimates from only two studies, ranging from 0.36% to 0.70%. The pooled prevalence of AS ranged from 0.20% (95% CI 0.10 to 0.34) to 0.25% (95% CI 0.18 to 0.33). A systematic review of population-based studies estimated the prevalence of AS at 23.8 cases per 10,000 in Europe (Dean et al., 2014). It is feasible that the prevalence figures reported in these reviews under-represented the true prevalence figures, due to a lack of true general population studies and continued under-recognition and under-diagnosis of axSpA.

1.4.3 Gender differences

Historically, AS has been considered to have a male predominance, with striking male to female ratios of up 10:1 reported in early studies (Rusman et al., 2018). More recently, that ratio has been revised down, closer to 3:1 (Rusman et al., 2018). In contrast, the distribution of nr-axSpA has virtually no difference between males and females (van Tubergen, 2014). The age of disease onset does not appear to differ between males and females (Rusman et al., 2018). A systematic review and meta-analysis published in 2017 examined the diagnostic delay in SpA and found a mean of 8.8 (7.4-10.1) years for females and 6.5 (5.6-7.4) years for males, a difference that was statistically significant (Jovani et al., 2017). This may relate to the differences in presenting symptoms, with men more likely to report typical IBP symptoms, and women more likely to report widespread pain, which made a delayed diagnosis twice as likely (Slobodin et al., 2011).

1.5 Clinical presentation

1.5.1 Back pain

The typical presenting symptom in axSpA is IBP (Sieper and Poddubnyy, 2017). The pain is usually insidious in onset and localised to the lower back or buttocks. It is typically associated with morning stiffness, which improves with activity and returns with rest. Exacerbation of the pain in the second half of the night is also common. People with axSpA can also complain of thoracic spinal pain, with cervical spine involvement usually occurring later in the course of disease. Anterior chest pain is also a feature of axSpA, affecting more than 40% of individuals with SpA (Wendling et al., 2013, Dougados et al., 2015).

Determining if low back pain (LBP) represents IBP can be challenging. LBP is extremely common in the general population: it is one of the top three causes of disability world-wide and the leading cause in Europe and North America (2018). The one-year prevalence of an episode of LBP lasting for at least a day is estimated to be 38% (Hoy et al., 2012) and the prevalence of chronic LBP in individuals between the age of 20 and 59 years is 19.6% (Meucci et al., 2015). However, the proportion of LBP cases which are IBP is low: the prevalence of IBP in a primary care population is estimated to be between 1.7% and 3.4% in the whole population, and 22.4% amongst individuals who have ever consulted with back pain (Hamilton et al., 2014). The prevalence of IBP related to SpA in a General Practitioner's (GP) office is estimated to be approximately 5% (Underwood and Dawes, 1995). Adding to the difficulty with diagnosing IBP, the recognition of the features of IBP is low amongst General Practitioners (GPs) (Jois et al., 2008).

Multiple attempts have been made to describe and define inflammatory back pain (IBP). The following clinical features have been considered as important in differentiating between IBP and other common causes of back pain (Sieper et al., 2009b):

- Age – onset of axSpA after the age of 45 years is exceedingly rare
- Duration of pain – non-inflammatory back pain is often self-limiting
- Onset of pain – non-IBP is often acute in onset
- Diurnal variation – pain and stiffness in axSpA-related IBP tends to be worst in the second half of the night and early morning
- Response to exercise – IBP responds well to exercise, a feature characteristic of many inflammatory conditions
- Location – alternating buttock pain can indicate inflammation of SI joints.

The Calin criteria (see Table 1-2) were the first attempt to classify IBP and were used in the ESSG classification criteria (Calin et al., 1977). Subsequently, the Berlin criteria were published in 2006 (see Table 1-2) (Rudwaleit et al., 2006) and ASAS criteria for IBP according to experts in 2009 (Table 1-2) (Sieper et al., 2009b). Despite this, chronic back pain, rather than IBP, was the required entry-criterion for the new ASAS classification criteria for axSpA (Figure 1-3) (Rudwaleit et al., 2009c), as the sensitivity of IBP for a diagnosis of axSpA was low, at approximately 70% (Rudwaleit et al., 2006).

Table 1-2: Three separate criteria for inflammatory back pain.

Calin Criteria (Calin et al., 1977)	Berlin Criteria (Rudwaleit et al., 2006)	ASAS expert criteria (Sieper et al., 2009b)
Age at onset < 40 years	Morning stiffness > 30 minutes	Age at onset < 40 years
Duration of back pain > 3 months	Improvement with exercise but not with rest	Pain at night, with improvement upon getting up
Insidious onset	Alternating buttock pain	Insidious onset
Associated with morning stiffness	Awakening in second half of night because of back pain	Improvement with exercise
Improvement with exercise		No improvement with rest
Criteria fulfilled if at least four of the five criteria are present, with specificity of 85% and sensitivity of 95%	*Criteria fulfilled if two or more parameters are fulfilled, with a sensitivity of 81% and specificity of 70%*	*Criteria fulfilled if four out of five parameters are present, with a sensitivity of 77% and specificity of 92%*

1.5.2 Peripheral disease

Individuals with axSpA have a higher risk of peripheral symptoms. Peripheral arthritis can affect up to half of individuals with axSpA (Ciurea et al., 2013, Heuft-Dorenbosch et al., 2004, Rudwaleit et al., 2009a). Enthesitis, or inflammation of the insertion sites of tendons and ligaments, is also common in SpA, with lifetime prevalence reported from 17% to 80% (Ciurea et al., 2013, Rudwaleit et al., 2009a, Glintborg et al., 2017); due to the close proximity between entheses and joints, there is an overlap between arthritis and enthesitis, and much of what is attributed clinically to arthritis has been shown on MRI studies to in fact be enthesitis (Schett et al., 2017). Dactylitis is more commonly seen as a manifestation of psoriatic arthritis (PsA) where it can affect up 50% of individuals (Kaeley et al., 2018); however, it also affects 6-8% of individuals with axSpA (de Winter et al., 2016). A meta-analysis explored the difference between AS and nr-axSpA in their prevalence of peripheral manifestations and found no significant difference between the two groups (de Winter et al., 2016).

1.5.3 Extra-articular manifestations (EAM)

Acute anterior uveitis (AAU), inflammatory bowel disease (IBD) and psoriasis (PsO) are three conditions over-represented in axSpA and are considered extra-articular manifestations (EAM) of the disease.

1.5.3.1 Acute anterior uveitis (AAU)

AAU is the most common of the EAM in axSpA, with a reported prevalence of 26-33% in two systematic reviews (Zeboulon et al., 2008, Stolwijk et al., 2015b). A lifetime history of uveitis was more common in AS than in nr-axSpA in a meta-analysis examining the differences between the two spectrums of disease (difference in pooled prevalence of 6.2%, CI 2.7 to 9.6%) (de Winter et al., 2016); this finding may have been a function of the longer disease duration in the AS group, as the risk of AAU is known to increase throughout the course of the disease (Stolwijk et al., 2015a). AAU affects men with AS more often than women (Zeboulon et al., 2008). Typically, attacks of AAU in axSpA are unilateral, with circumlimbal hyperaemia, pain, photophobia and visual impairment, with subsequent attacks often affecting the other eye (Taurog et al., 2016). Attacks have an acute onset, often with a one- to two-day prodrome, but the visual prognosis is excellent, with most individuals recovering full vision within two months (Rosenbaum, 2015). Genetic loci have been identified which affect the predisposition of an individuals with AS to uveitis separately to joint disease (Robinson et al., 2015, Martin et al., 2005).

1.5.3.2 Psoriasis (PsO)

PsO can affect approximately 10% of individuals with axSpA (Stolwijk et al., 2015b, Exarchou et al., 2015, de Winter et al., 2016), with no significant difference in those with AS compared to nr-axSpA.

1.5.3.3 Inflammatory bowel disease (IBD)

IBD affects 5-10% of individuals with axSpA (Stolwijk et al., 2015b). Crohn's disease is more common than Ulcerative Colitis (Taurog et al., 2016). However, endoscopic and histologic gut inflammation has been demonstrated in up to half of axSpA individuals (Lee et al., 1997, Leirisalo-Repo et al., 1994, Van Praet et al., 2013). Faecal calprotectin is a non-specific marker for gut inflammation, which is related to disease activity in individuals with AS, but not with gut symptoms (Klingberg et al., 2012a). In a five-year longitudinal study, higher faecal calprotectin levels at baseline were associated with the development of Crohn's disease, as well as more severe AS disease clinically, but without any relationship to gut symptoms, suggesting that inflammation in the gastrointestinal tract and musculoskeletal system are linked (Klingberg et al., 2017).

1.6 Pathogenesis

Most pathogenesis studies to date have focused on AS rather than axSpA. Studies performed on monozygotic twins and familial aggregation studies suggest that AS has a heritability of above 90% (Brown et al., 1997, van der Linden et al., 1983). HLA-B27 positivity is also strongly linked with AS, occurring in only about 5% of the general population but more than 90% of individuals with AS. However, despite this strong association, HLA-B27 contributes only 33% of the total heritability of AS (Bowness, 2015).

1.6.1 HLA-B27

HLA-B27, a class 1 surface antigen encoded by the major histocompatibility complex (MHC), is found in 74 to 89% of individuals with axSpA (Poddubnyy and Sieper, 2014). Part of the differences seen in the prevalence of axSpA worldwide can be explained by the different prevalence of HLA-B27. The prevalence of HLA-B27 is highest in the Pawaia tribe in Papua New Guinea (53%) and the Haida indigenous Americans on Queen Charlotte Islands in Western Canada (50%), and lowest in Arab countries (2-5%) and Japan (1%) (Stolwijk et al., 2012). In Europe, HLA-B27 varies from 4-13% in the west and 15-25% in Northern Scandinavia, with approximately 90% of individuals with AS HLA-B27 positive (Stolwijk et al., 2012). However, in black populations, HLA-B27 occurs in less than 60% of cases of AS (Khan, 1978) and AS is almost non-existent in South-American Indians and Australian Aborigines (Khan, 1995). The association between HLA-B27 and AS is weaker in the Middle East than Europe (al-Arfaj, 1996, Uppal et al., 2006).

The MHC is a cluster of genes which is responsible for encoding cell membrane glycoproteins which display peptide antigen to T cells (Janeway et al., 2005). There are two types of MHC molecules: Class 1 and Class 2. Class 1 and Class 2 are very similar in their structure but differ in the source of peptides that they bind and display on the surface. The class 1 molecules bind peptide fragments from viral-infected cells, whereas class 2 molecules bind peptides originating from intracellular vesicles, such as in bacterial-infected cells. The MHC contains many different MHC Class 1 and MHC Class 2 genes. Therefore, each individual contains a unique range of peptide-binding specificities.

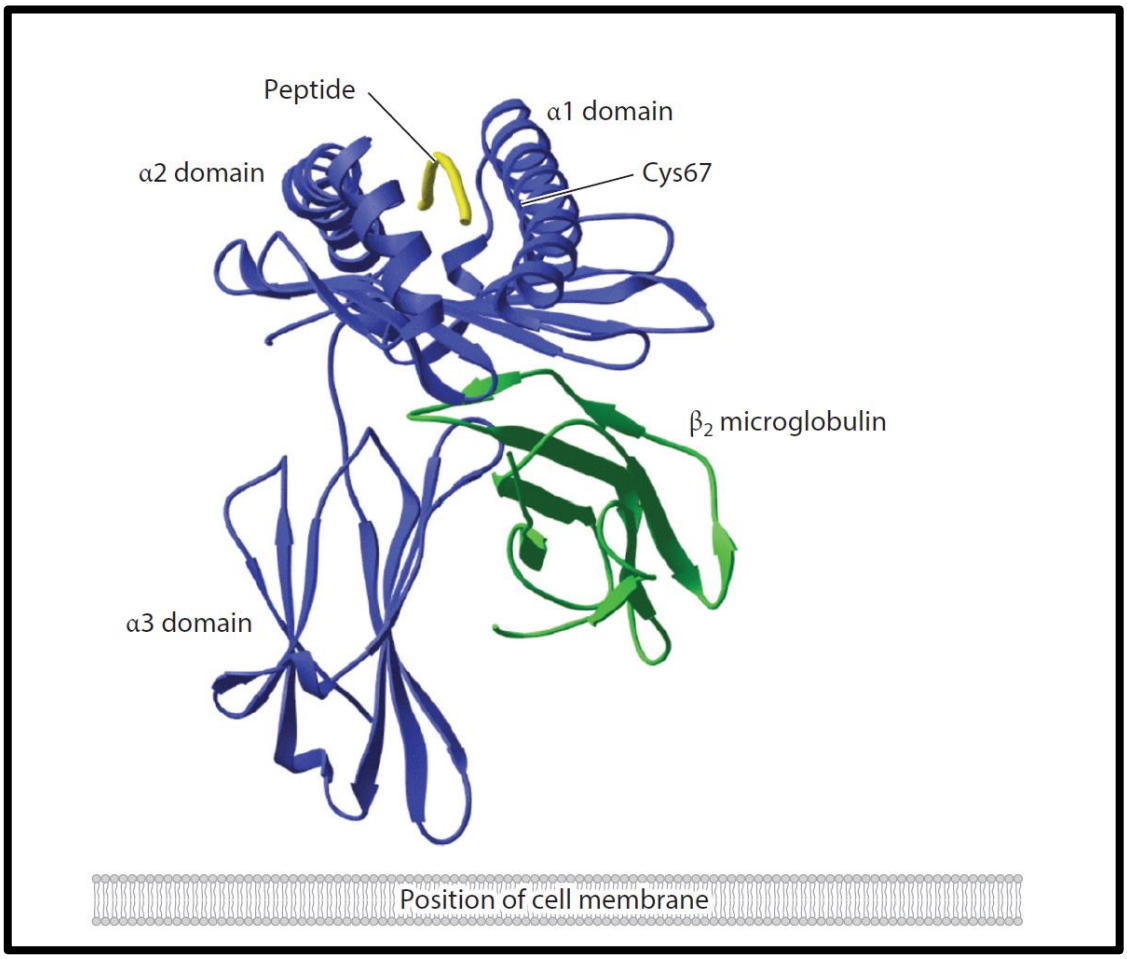
The MHC is also known as the human leukocyte antigen (HLA) (Figure 1-5). HLA-B27 belongs to the MHC Class 1 molecules (Bodis et al., 2018) and is encoded on chromosome 6 (Bowness, 2015). There are three main HLA Class 1 genes: A, B and C, which encode molecules which are

expressed on the surface of nucleated cells. The main role of HLA-B27 is to present intracellular peptides to the T cell receptor of cytotoxic T cells, with one of three outcomes: 1) tolerance of 'self' antigens; 2) activation of cell-mediated immunity; 3) maladaptive autoimmune response if 'self' is not recognised (Bodis et al., 2018).

The HLA-B27 allomorph is one of the most common B alleles in Caucasians. The structure of HLA-B27 was the second to be recognised, after HLA-A2. The peptide-binding groove contains a unique combination of residues, which differentiates it from other HLA molecules and includes a glutamic acid residue at position 45 and cysteine at 67 (Bowness, 2015). The heavy chains of HLA-B27 are made in the endoplasmic reticulum (ER). They fold into a complex with ß2-microglobulin ($ß_2$m) and intracellular peptides within the ER. This complex then moves to the surface of the cell, where they are recognised by cytotoxic T-lymphocytes.

There are more than 140 subtypes of HLA-B27 recognised (Taurog et al., 2016) – there are some differences in the sequence of amino acids between the subtypes, but they all share a strong preference for arginine at the second position of the bound peptide. Additionally, the structural, peptide-binding and antigenic features are broadly similar. They are labelled from HLA-B*2701 to HLA-B*27106, according to their deoxyribonucleic acid (DNA) sequence. The most common subtype in Caucasian populations is B*2705 (Bodis et al., 2018). Many of the HLA-B27 subtypes have been associated with a risk of developing AS. B*2702 is strongly linked with AS (Frankenberger et al., 1997), particularly in the Mediterranean population (Khan, 2013). B*2704 also has a strong association with AS in Chinese populations (Lin et al., 1996). Associations between B*2705 and B*2707 and AS are also clear in the literature (Taurog et al., 2016). In contrast, B*2706 and B*2709 are not associated with AS (Khan, 2013).

Figure 1-5: Molecular structure of HLA-B27 (Bowness, 2015).



Exactly how HLA-B27 predisposes to AS is as of yet not fully understood, but several hypotheses have been put forward. There are three specific features of HLA-B27 which differentiate it from other MHC class 1 molecules and may explain part of the role HLA-B27 plays (Colbert et al., 2014):

1. **Peptide binding specificity**

It is proposed that the specific sequence of amino acids found in the peptide-binding groove of HLA-B27 might bind a peptide which elicits a cytotoxic T-cell response cross-reactive with a B27/self-peptide combination, i.e. molecular mimicry (Bowness, 2015). This is termed the *arthritogenic peptide hypothesis*. However, specific triggering antigens have not yet been consistently identified.

2. Propensity to misfold

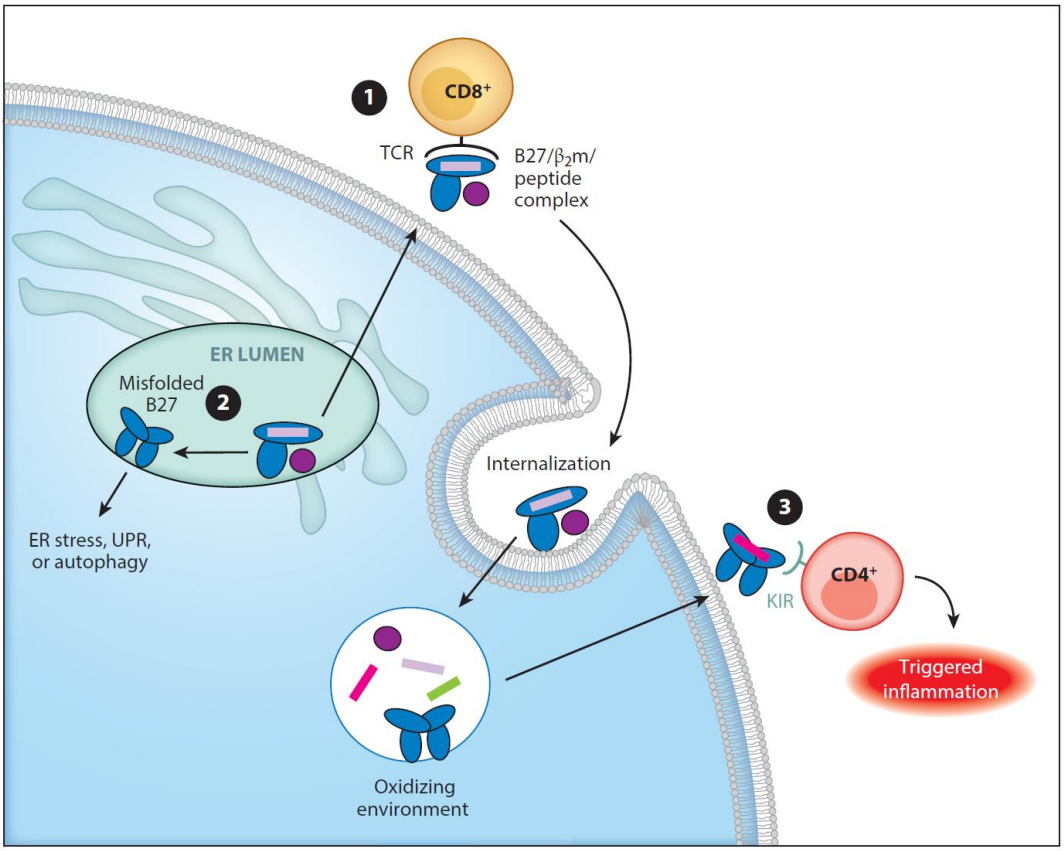
Another unique feature of HLA-B27 is that it misfolds, which could lead to ER stress. It was recognised in the 1990s that HLA-B27 is capable of forming homodimers, which then led to the discovery that HLA-B27 misfolds in the ER. This subsequently leads to degradation in the cytosol. It is thought that the specific sequence of amino acids in the B pocket of the peptide-binding groove is what leads to a propensity for HLA-B27 to misfold, as replacing the peptides with the sequence found in HLA-A2 corrects this tendency to misfold (Bowness, 2015, Colbert et al., 2014). In HLA-B27 transgenic rats, HLA-B27 misfolding is seen to occur and correlates with an increased production of interleukin (IL)-23 (DeLay et al., 2009). Therefore, this indicates that HLA-B27 may be in a position to cause a pro-inflammatory ER stress response (Turner et al., 2005). However, much of the research is currently in transgenic rats, with no strong evidence in humans as of yet. This is termed the *HLA-B27 misfolding hypothesis.*

3. Tendency to form heavy chain homodimers during cell surface recycling.

The third feature involves HLA-B27's ability to form disulphide-bonded homodimers, $B27_2$, which is atypical for HLA Class 1 molecules. B27 free heavy chains are also expressed at the cell surface. $B27_2$ and the free heavy chains bind to receptors on T, natural killer (NK) and myeloid cells. However, the affinity of the homodimeric $B27_2$ and the free heavy chains are different to the traditional heterotrimeric complexes, leading to proinflammatory effects on NK and T cells It is also associated with a T-helper cell 17 (Th17) phenotype in AS (Bowness, 2015). Therefore, it has been postulated that this surface expression of $B27_2$ contributes to the pathogenesis of AS, termed the *cell surface B27 free heavy chain expression and immune recognition hypothesis*.

An overview of these three hypotheses can be seen in Figure 1-6.

Figure 1-6: Overview of three hypotheses outlining the role of HLA-B27 in the pathogenesis of axSpA: (1) Arithrogenic peptide hypothesis, (2) HLA-B27 misfolding hypothesis, and (3) Cell surface B27 free heavy chain expression and immune recognition hypothesis (Bowness, 2015).



1.6.2 Other genetics of AS

Genome-wide association studies (GWAS) based on single-nucleotide polymorphisms (SNPs) have identified over 100 genetic variants associated with AS (Ranganathan et al., 2017). Twenty percent of the genetic heritability was explained by MHC variants, which includes HLA-B27, and 7% by non-MHC variants (Ellinghaus et al., 2016). Two other genetic loci have been identified as of potential interest: endoplasmic reticulum aminopeptidase (ERAP) and the IL-23 receptor. ERAP has a role in preparing peptides before MHC Class 1 presentation to immune effector cells (Cortes et al., 2013). Genes that affect the IL-23 receptor cause activation of the T-helper cells, which lead to the secretion of IL-17 and other proinflammatory cells (Coffre et al., 2013).

1.7 Imaging in axSpA

1.7.1 X-ray of SI joints in axSpA

As the sacroiliac joints (SIJ) are central to the disease process in axSpA, imaging of the joints has a pivotal role in diagnosis. ASAS recommends performing an x-ray of the whole pelvis when assessing for sacroiliitis, as this also allows the hip joints to be visualised (Sieper et al., 2009a). The severity of sacroiliitis is included in the mNY criteria (van der Linden et al., 1984), graded as follows (Sieper et al., 2009a):

- Grade 0: normal
- Grade 1: suspicious changes
- Grade 2: minimal abnormality – small localised areas with erosions or sclerosis, without alteration in the joint width
- Grade 3: unequivocal abnormality – moderate or advanced sacroiliitis with one or more of erosions, evidence of sclerosis, widening, narrowing or partial ankylosis
- Grade 4: severe abnormality – total ankylosis.

X-rays of the SIJ are recommended as the first imaging method in suspected SpA (Mandl et al., 2015), as up to 50% of individuals with a disease duration of less than three years will have radiographic sacroiliitis, negating the need for further investigations (Poddubnyy et al., 2012).

However, there are limits to the use of x-rays in the diagnosis of axSpA, as structural changes can take months to years to occur (Sieper and Poddubnyy, 2017), and not everyone with non-radiographic axSpA develops into AS (Keat et al., 2017). In addition, interpretation of SI joint x-rays is challenging, with considerable inter-reader variation (van Tubergen et al., 2003, Christiansen et al., 2017).

1.7.2 MRI of SI joints

MRI is now an invaluable tool in the assessment of individuals with AS, and is the next step in the investigation of a person with suggestive symptoms but normal x-rays of the SI joints (Mandl et al., 2015). It is important that the correct sequences of MRI are performed, to minimise the risk of not detecting inflammation when it is in fact present. Active inflammation is best visualised using fat-saturated T2-weighted turbo spin-echo sequence (such as a short tau inversion recovery (STIR) sequence) (Sieper et al., 2009a). This allows identification of even very small collections of fluid. Chronic changes, including erosions, sclerosis, ankyloses and fatty lesions, are best visualised using T1-weighted sequence (Sieper et al., 2009a). Administrating gadolinium contrast

medium in a T1-weighted sequence with fat saturation can also allow detection of osteitis; however, it is rarely needed as it usually does not add any information to that provided by the STIR sequence (Sieper and Poddubnyy, 2017).

The updated ASAS definition of 'active sacroiliitis' on MRI (Lambert et al., 2016) mandates that bone marrow inflammation must be present, along with the following features:

1. Bone marrow oedema on a T2-weighted sequence sensitive for water e.g. STIR sequence, or contrast-enhanced T1-weighted sequence
2. Inflammation must be clearly present
3. MRI appearance must be highly suggestive of SpA.

In the absence of bone marrow oedema, structural lesions alone (e.g. fat metaplasia, sclerosis, erosion, ankylosis) does not meet the criteria of active sacroiliitis on MRI (Lambert et al., 2016).

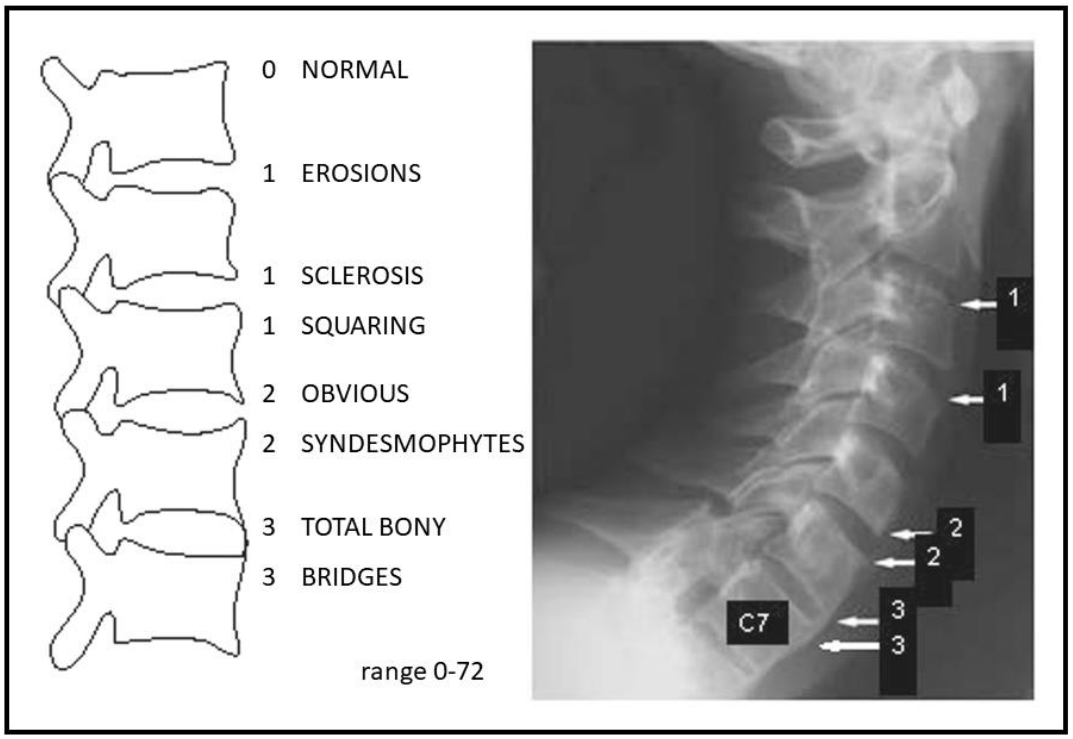
1.7.3 Imaging of spine

Imaging of the spine is not needed for early diagnosis, as the SI joints are more commonly affected and adding MRI of the spine to the assessment has not been shown to improve confidence in the diagnosis (Weber et al., 2015). However, x-rays are the best method to detect chronic changes of the spine, including syndesmophytes, with the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) (see Figure 1-7) (Creemers et al., 2005) the ASAS preferred method for scoring changes (Sieper et al., 2009a). A combined ASAS/OMERACT study group have also published clear definitions of a positive MRI of the spine, for both inflammatory lesions (spondylitis) and structural changes (fat deposition), which are suitable for use both in daily clinical practice and clinical studies (Hermann et al., 2012).

1.7.4 Other imaging modalities

Previously scintigraphy played a prominent role in assessing for inflammation in individuals with axSpA. However, the sensitivity and specificity for detecting inflammation with this imaging modality was limited and has been superseded by MRI. Therefore, it is not used routinely in current day management (Mandl et al., 2015). Computed tomography (CT) has a role in detecting chronic bony changes, being superior to both x-ray and MRI, but due to the high level of radiation associated with CT, it is not often used. Additionally, it has no role in detecting acute inflammation. Its use should be reserved for otherwise inconclusive cases (Mandl et al., 2015).

Figure 1-7: Sample modified Stoke Ankylosing Spondylitis Spinal Score scoring, from zero to three, for spinal vertebral edges (van der Heijde et al., 2018).



1.8 Diagnostic pitfalls

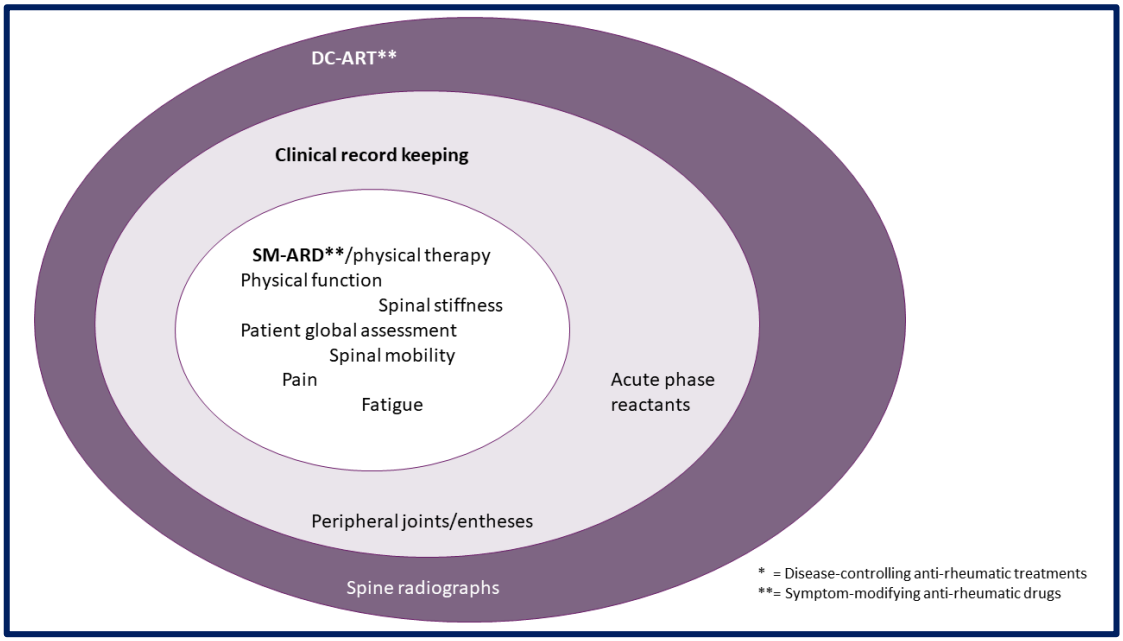
There are some changes of the spine which can be confused for AS and must be considered when making a diagnosis. Diffuse idiopathic skeletal hyperostosis (DISH) is a systemic condition, affecting 10% of the population above 50 years of age (Mader et al., 2017). Although it shares some features with AS (both cause bony formation and calcification of spinal ligaments, and have an increased risk of vertebral fractures), they are in reality very different diseases. DISH commonly occurs in elderly people, in comparison to the young onset by which AS is characterised. The structural changes of DISH can be very marked, with flowing osteophytes affecting the spine. It has a particular predilection for the thoracic spine. individuals with severe changes of DISH can be asymptomatic, but there are strong associations with metabolic and cardiovascular disease.

1.9 Outcome assessment

In 1999, the ASAS-Outcome Measures in Rheumatology (OMERACT) group published core sets of variables to assess the outcome of AS, providing the minimum domains that should be included as standardised end-points in trials and clinical record keeping (see Figure 1-8) (van der Heijde et al., 1999). They defined three core sets:

- Disease-controlling antirheumatic treatments (DC-ART)
- Clinical record keeping
- Symptom-modifying anti-rheumatic drugs (SM-ARD).

Figure 1-8: Assessment of SpondyloArthritis (ASAS)/Outcome Measures in Rheumatology Clinical Trials (OMERACT) core domains for ankylosing spondylitis (van der Heijde et al., 1999).



In 2009, the core sets were adapted slightly to comply with and allow endorsement by the World Health Organisation (WHO) International Classification of Functioning, Disability and Health (ICF) framework (World Health Organization, 2001). This framework allows the assessment of the impact of axSpA, both on individuals and populations, using the bio-psycho-social model (Stucki and Ewert, 2005, Boonen et al., 2010). Both Comprehensive ICF Core Sets (C-ICF-CS) to guide multidisciplinary assessments and facilitate research on functioning and health, and Brief ICF Core Sets (B-ICF-CS) to describe individuals during clinical studies (see Table 1-3), were developed (Boonen et al., 2010).

Table 1-3: International Classification of Functioning, Disability and Health (ICF) categories included in the brief ICF core set for Ankylosing Spondylitis (Boonen et al., 2010).

ICF component	ICF code	ICF category title
Body functions	b280	Sensation of pain
	b710	Mobility of joint functions
	b780	Sensations related to muscles and movement functions
	b130	Energy and drive functions
	b134	Sleep functions
	b152	Emotional functions
	b455	Exercise tolerance functions
Body structures	S760	Structure of trunk
	s740	Structures of pelvic region
	s770	Additional musculoskeletal structures related to movement
	s750	Structure of lower extremity
Activities and participation	d230	Carrying out daily routine
	d410	Changing basic body position
	d450	Walking
	d845	Acquiring, keeping and terminating a job
	d850	Remunerative employment
	d760	Family relationships
	d920	Recreation and leisure
	d475	Driving
Environmental factors	e110	Products or substances for personal consumption
	e3	Support and relationships

Ultimately, these core sets measure all aspects of outcome in AS individuals and the instruments recommended to assess each domain are outlined in Table 1-4.

Table 1-4: Recommended instruments for each domain of the Assessment of SpondyloArthritis (ASAS)/Outcome Measures in Rheumatology Clinical Trials (OMERACT) core sets (Sieper et al., 2009a).

Domain	Instrument
Function	BASFI
Pain	NRS/VAS (last week/spine/at night/due to AS)
	NRS/VAS (last week/spine/ due to AS)
Spinal mobility	Chest expansion
	Modified Schober
	Occiput to wall
	Cervical rotation
	Lateral spinal flexion or BASMI
Patient global	NRS/VAS (global disease activity last week)
Peripheral joints and entheses	Number of swollen joints (44-joint count)
	Validated enthesitis scores, such as MASES, San Francisco and Berlin
X-ray spine	Lateral lumbar spine and lateral cervical spine
Stiffness	NRS/VAS (duration of morning stiffness/spine/last week)
Acute phase reactants	CRP or ESR
Fatigue	Fatigue question BASDAI

AS: Ankylosing Spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; NRS: numerical rating score 0-10; VAS: visual analogue scale 0-100.

1.9.1 Overview of instruments to assess disease outcomes

1.9.1.1 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (Garrett et al., 1994) is a patient-reported outcome (PRO) used to assess disease activity (Appendix D). It contains six items and assesses levels of back pain, fatigue, peripheral joint pain and swelling, localised tenderness, and the duration and severity of morning stiffness. Each item is scored on a scale of zero to ten, where higher scores indicate worse disease. Question four and five are averaged, as both assess morning stiffness. This result is then averaged with the other four questions to provide a score out of ten (Zochling, 2011). Both internal consistency and test-retest reliability are good (Garrett et al., 1994, Haywood et al., 2002), with acceptable content validity (Zochling, 2011). A BASDAI score of four or greater is considered active disease, taken as the cut-off to consider starting biologic therapy (Braun et al., 2003). A minimum clinically important improvement (MCII) of 1.1 for BASDAI is recommended to evaluate the effectiveness of treatment (Kviatkovsky et al., 2016).

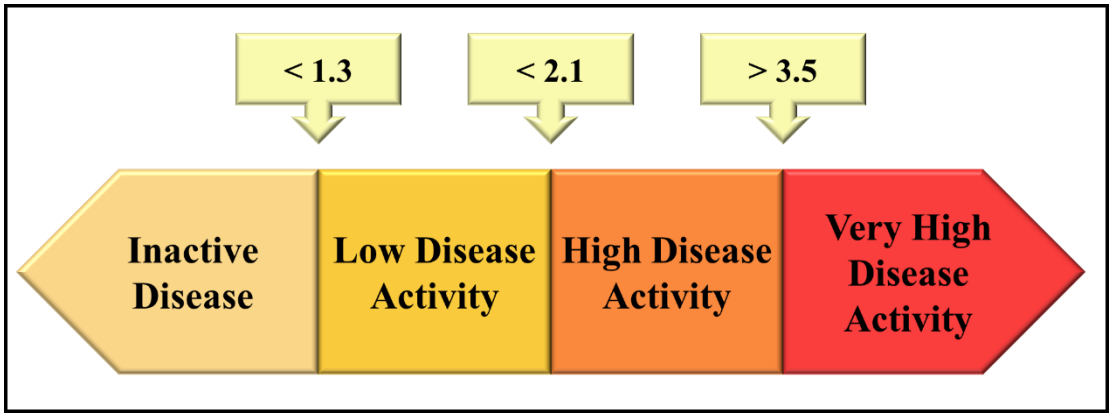
1.9.1.2 Ankylosing Spondylitis Disease Activity Score (ASDAS)

ASAS developed the Ankylosing Spondylitis Disease Activity Score (ASDAS), which is a composite measure incorporating both subjective PROs and an objective measure of disease activity, either C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) (Lukas et al., 2009, van der Heijde et al., 2009a). The ASDAS-CRP version is the preferred version by ASAS. The score contains five items: back pain, duration of morning stiffness, peripheral joint pain and/or swelling, plus CRP or ESR. It is calculated as outlined Table 1-5. Reliability data is not yet available for these scores (Zochling, 2011). ASDAS has shown to be effective at discriminating different levels of disease activity and detecting change (van der Heijde et al., 2009a, van der Heijde et al., 2012). Cut-offs for different levels of disease activity are well-defined (see Figure 1.9) (Machado et al., 2011). A change in ASDAS of 1.1 units or more indicates a clinically important improvement and a change of 2.0 units or greater indicates a major improvement (Machado et al., 2011). ASDAS also performs well in nr-axSpA (Fernandez-Espartero et al., 2014, Kilic et al., 2015).

Table 1-5: Calculation of the Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein and Erythrocyte Sedimentation Rate (Lukas et al., 2009, van der Heijde et al., 2009a)

$ASDAS_{CRP}$ = 0.121 x *total back pain* + 0.110 x *patient global* + 0.073 x *peripheral pain/swelling* + 0.058 x *duration of morning stiffness* + 0.579 x Ln(*CRP*+1)
$ASDAS_{ESR}$ = 0.113 x *patient global* + 0.293 x $\sqrt{}$*ESR* + 0.086 x *peripheral pain/swelling* + 0.069 x *duration of morning stiffness* + 0.079 x *total back pain*
ASDAS: Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Ln: natural logarithm. *$ASDAS_{CRP}$ is preferred, but $ASDAS_{ESR}$ is used if CRP is not available.*

Figure 1-9: Selected cut-offs for disease activity states using the Ankylosing Spondylitis Disease Activity Score (Machado et al., 2011).



1.9.1.3 Bath Ankylosing Spondylitis Functional Index (BASFI)

The Bath Ankylosing Spondylitis Functional Index (BASFI) is a PRO designed to assess physical functioning (Calin et al., 1994). It contains ten items which assess the functional anatomy of individuals and the ability to cope with everyday life (see Appendix D). Each item is measured on a scale of zero to ten, where higher numbers reflect more impairment. The ten items are averaged to provide an overall score. Internal consistency is excellent and test-retest reliability is good (Zochling, 2011). The MCII is a change in BASFI of 0.6 units (Kviatkovsky et al., 2016).

1.9.1.4 Health Assessment Questionnaire (HAQ)

The Health Assessment Questionnaire (HAQ) is a PRO (Fries et al., 1980) which assesses physical functioning. Each question is scored on a scale of zero to three, with zero indicating no impairment and three indicating higher impairment or worse function. Test-retest reliability and content validity are good (Zochling, 2011).

1.9.1.5 Ankylosing Spondylitis Quality of Life (ASQoL)

The Ankylosing Spondylitis Quality of Life (ASQoL) tool (Doward et al., 2003) was developed with the purpose of assessing health-related quality of life from the individual's perspective. It is a PRO, with questions relating to the impact of axSpA on sleep, mood, motivation, coping, activities of daily living, independence, relationships and social life (see Appendix D). All items are yes/no, with each 'yes' answer scoring one point. The points are summed, and the result is the overall score, on a scale of zero to eighteen. Higher scores indicating greater impairment of health-related quality of life. Internal consistency and test-retest consistency is good (Zochling, 2011). An improvement of two points is the MCII for ASQoL (Richard et al., 2018).

1.9.1.6 Bath Ankylosing Spondylitis Metrology Index (BASMI)

The Bath Ankylosing Spondylitis Metrology Index (BASMI) (Jenkinson et al., 1994) was developed to quantify spinal mobility in individuals with AS. It assesses lateral lumbar flexion, tragus-to-wall distance, lumbar flexion, intermalleolar distance and cervical rotation. Each item is scored from zero to ten based on defined cut-points (Appendix D) and averaged to give a final score. Higher scores reflect more significant impairment of spinal mobility. Inter-rater and intra-rater reliability are both good (Zochling, 2011). BASMI has been shown to discriminate between

individuals with and without radiographic change (Wanders et al., 2005). It is also able to detect change (Jenkinson et al., 1994).

1.9.1.7 Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS)

In 1991, the Stoke Ankylosing Spondylitis Spinal Score (SASSS) was developed, which quantified radiological damage on the anterior and posterior sites of the lumbar spine and ranged from 0-72 (Taylor et al., 1991). It assessed the lower border of T12, all five lumbar vertebrae and the upper sacrum, using lateral spinal x-rays. This was modified by (Creemers et al., 2005) and called the modified SASSS (mSASSS). The anterior sites of the same lumbar vertebrae are scored. In addition, cervical vertebrae are scored (see Figure 1-7), from the upper border of T1 to lower border of C2. Using this measure, zero indicates normal spine and 72 a completely ankylosed, or 'bamboo' spine (Creemers et al., 2005). It has been shown to be reliable, able to detect change and has an acceptable constructive validity (Creemers et al., 2005). The mSASSS is considered the most appropriate method to assess radiographic change (Wanders et al., 2004, Ramiro et al., 2018).

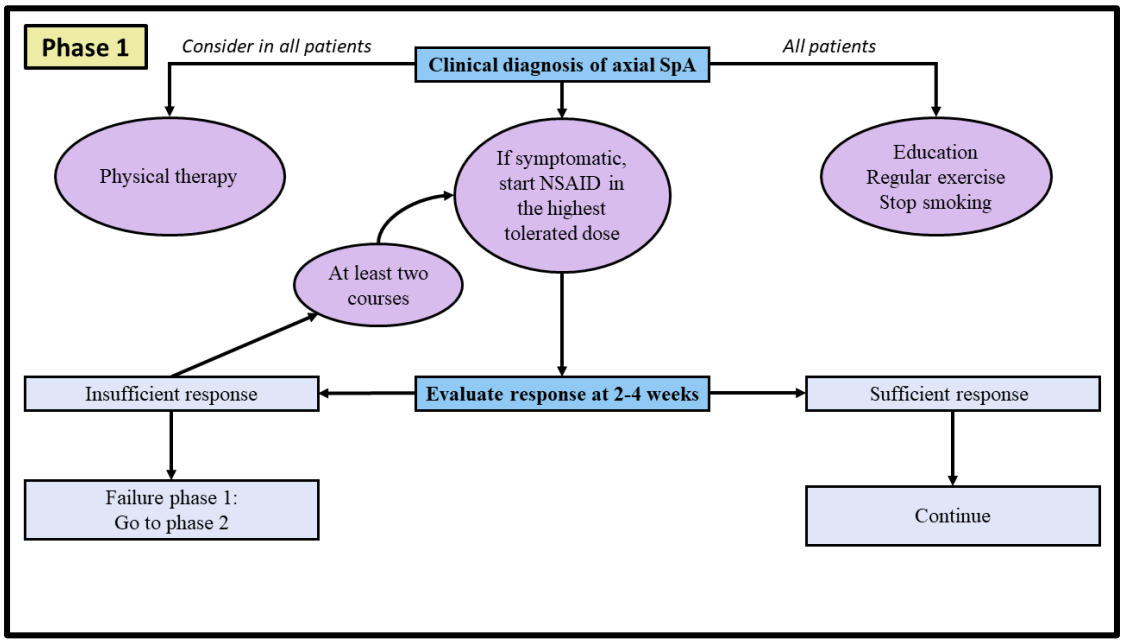
1.10 Management of axSpA

In 2016, the ASAS/European League Against Rheumatism (EULAR)n updated recommendations for the management of axSpA were published (van der Heijde et al., 2017). These were updated from recommendations published in 2010 (Braun et al., 2011), with the aim of catering for the whole spectrum of disease, including individuals with AS and nr-axSpA, and addressing all aspects of management, pharmacological and non-pharmacological. These recommendations are summarised in an algorithm in Figure 1-10.

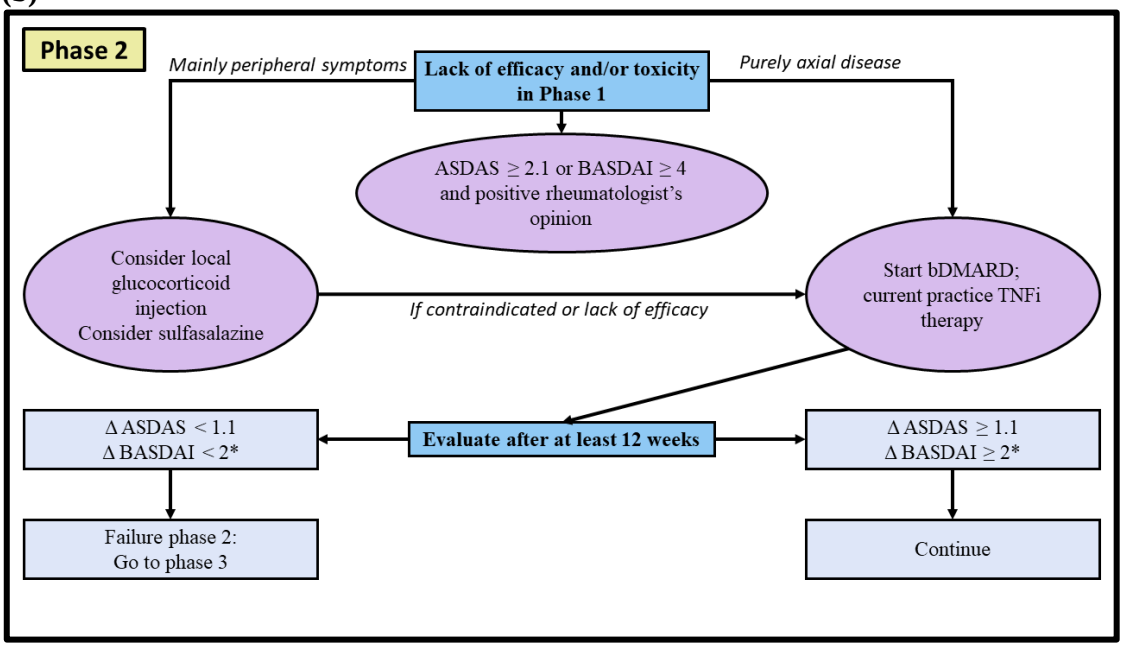
A treat-to-target approach is recommended in the management of axSpA (Smolen et al., 2014), with remission the main target, and low disease activity an alternative target (Figure 1-9). A low ASDAS score can be used to define remission (Machado et al., 2011); however, controversy exists as the efficacy of a treat-to-target strategy hasn't yet been tested in prospective cohorts (Machado and Deodhar, 2019).

Figure 1-10: Algorithm based on the Assessment of SpondyloArthritis Society (ASAS)/European League Against Rheumatism (EULAR) recommendations for the management of axial spondyloarthritis; incorporating (a) Phase 1, (b) Phase 2, and (c) Phase 3. Adapted from (van der Heijde et al., 2017). ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease-modifying antirheumatic drug; TNFi, tumour necrosis factor inhibitor; IL17-inhibitor, interleukin-17 inhibitor. *Either BASDAI or ASDAS, but the same outcome per individual.

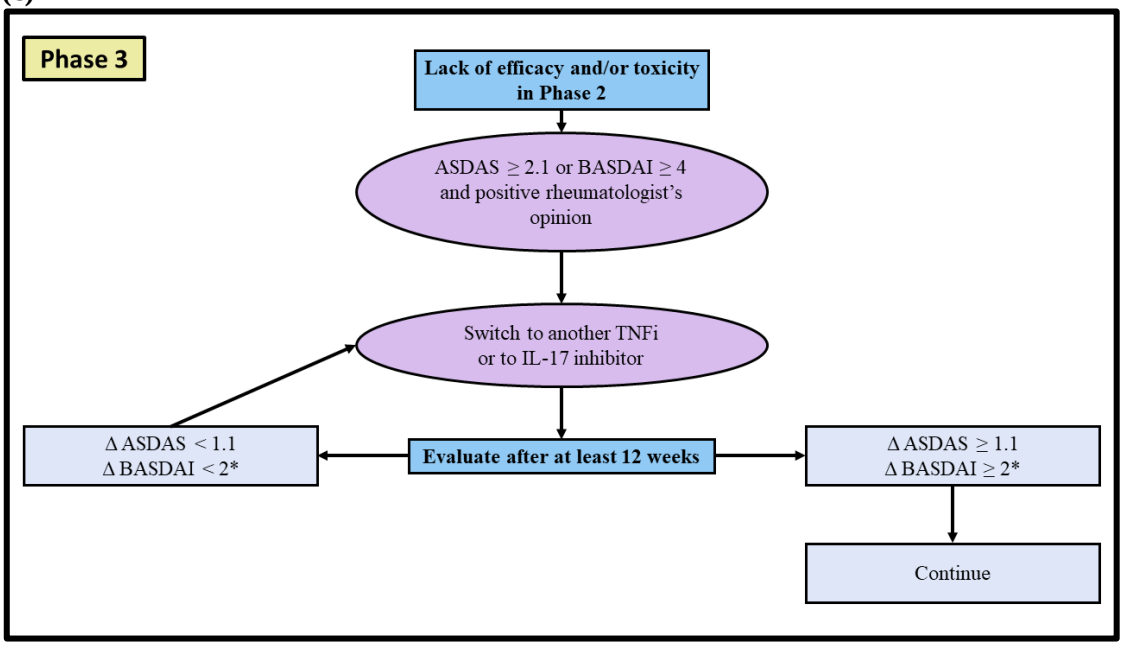
(a)



(b)


Phase 2
Mainly peripheral symptoms
Lack of efficacy and/or toxicity in Phase 1
Purely axial disease
ASDAS ≥ 2.1 or BASDAI ≥ 4 and positive rheumatologist's opinion
Consider local glucocorticoid injection
Consider sulfasalazine
If contraindicated or lack of efficacy
Start bDMARD; current practice TNFi therapy
Δ ASDAS < 1.1
Δ BASDAI < 2*
Evaluate after at least 12 weeks
Δ ASDAS ≥ 1.1
Δ BASDAI ≥ 2*
Failure phase 2: Go to phase 3
Continue

(c)


Phase 3
Lack of efficacy and/or toxicity in Phase 2
ASDAS ≥ 2.1 or BASDAI ≥ 4 and positive rheumatologist's opinion
Switch to another TNFi or to IL-17 inhibitor
Δ ASDAS < 1.1
Δ BASDAI < 2*
Evaluate after at least 12 weeks
Δ ASDAS ≥ 1.1
Δ BASDAI ≥ 2*
Continue

1.10.1 Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are effective in reducing pain and stiffness in individuals with axSpA (Kroon et al., 2015) and so are recommended as the first line in pharmacological treatment (van der Heijde et al., 2017). They appear to be equally effective in AS and nr-axSpA (Baraliakos et al., 2017). There is no difference in the effectiveness of individual NSAIDs (Song et al., 2008). They have a quick onset of efficacy (Kroon et al., 2015), with individuals generally responding within two weeks, although sustained improvement is seen for the first 24 weeks (Sieper and Poddubnyy, 2017). NSAIDs appear more effective if started early in the disease, with better response rates than individuals with long-standing disease (Sieper et al., 2008, Sieper et al., 2014, van der Heijde et al., 2005).

The safety profile of NSAIDs is a concern. A systematic review did not show any increased adverse events compared to placebo over twelve weeks (Kroon et al., 2015). However, celecoxib and diclofenac both increased the risk of cardiovascular death in a meta-analysis of 754 trials comparing NSAIDs to placebo or other NSAIDs and all NSAIDs increased the risk of heart failure (Bhala et al., 2013).

1.10.2 Tumour necrosis factor-inhibitors (TNFi)

The major breakthrough in the management of axSpA came with the recognition that tumour necrosis factor (TNF)-inhibition was successful in active refractory disease (Van den Bosch et al., 2000, Breban et al., 2002, Brandt et al., 2000, Brandt et al., 2004). Since then, TNF-inhibitors have shown sustained efficacy, not only on disease activity, but also on function and quality of life (Baraliakos et al., 2013, Arends et al., 2017, Davis et al., 2005, van der Heijde et al., 2009c, van der Heijde et al., 2015, Braun et al., 2008). To date, five TNF-inhibitors are licenced for the treatment of axSpA: adalimumab, etanercept, certolizumab, infliximab and golimumab. TNF-inhibitors have also been shown to be effective in the treatment of nr-axSpA (Sieper et al., 2013, Callhoff et al., 2015). TNF-inhibitors are safe, with the risk of serious infection not significantly increased (Wang et al., 2018).

There are some limitations to the use of TNF-inhibitors. Up to 20-40% of individuals may not respond to TNF-inhibition (Dougados and Baeten, 2011), although many subsequently respond to an alternative TNF-inhibitor (Coates et al., 2008). individuals do not achieve sustained remission on TNF-inhibitors, with nearly all relapsing if the biologic is withdrawn, although a tapering strategy may be effective in many cases (Navarro-Compan et al., 2016). Lastly, the effect of TNF-inhibition on structural damage is still unclear, as will be explained in more detail in Chapter 3.

1.10.3 Interleukin-17 inhibition

Secukinumab, an interleukin (IL)-17 inhibitor, has recently been approved for use in the treatment of axSpA. It has been shown to have a sustained effect on the signs and symptoms of axSpA and is well tolerated (Marzo-Ortega et al., 2017, Braun et al., 2017, Baraliakos et al., 2018). It also appears to have a positive effect on radiographic progression (Aouad et al., 2019). In addition, in MEASURE 2, secukinumab was shown to be effective in the treatment of individuals who had responded inadequately to TNF-inhibitors (Sieper et al., 2017).

1.11 Outcomes in axSpA

1.11.1 Mortality in axSpA

In past decades, radiation therapy of the spine was employed as a treatment for AS, with treated individuals experiencing an excess of four to six deaths per 1000 patients from leukaemia and other cancers (Brown and Doll, 1965). However, studies performed in the 1970s and 1980s showed that increased mortality rates were seen in all individuals with AS, not just those treated with radiation (Radford et al., 1977, Khan et al., 1981).

More recent data continues to demonstrate that mortality is increased when compared to controls (Braun and Pincus, 2002, Buschiazzo et al., 2016, Wang and Ward, 2018, Prati et al., 2017, Haroon et al., 2015, Lehtinen, 1993). In a population-based registry study in Sweden, Exarchou et al demonstrated that individuals with AS had a higher risk of death compared to matched controls (HR 1.6, 95% CI 1.44 to 1.77), and less education, comorbidities and a history of hip replacement predicted death (Exarchou et al., 2016). Some of the excess mortality in axSpA can be explained by direct consequences such as death due to neurological deficit from vertebral fractures (Westerveld et al., 2014, Wysham et al., 2017). Cardiovascular disease has also been demonstrated to be a leading cause of death in individuals with AS (Bakland et al., 2011, Exarchou et al., 2016, Haroon et al., 2015). In addition, more active disease as measured by CRP levels was associated with increased mortality (OR 2.68) in a case-control cohort study by Bakland et al (Bakland et al., 2011). A population-based cohort study subsequently demonstrated a lower risk of mortality in AS individuals who were started on statins (Oza et al., 2017). No increase in cancer risk has been seen in individuals not treated with radiation (a treatment modality no longer used) (Feltelius et al., 2003, Bakland et al., 2011). A systematic review found no significantly increased risk of serious infection in AS, either with or without TNFi treatment (Fouque-Aubert et al., 2010).

1.11.2 Morbidity in axSpA

A comorbidity can be defined as 'any distinct additional clinical entity that has existed or that may occur during the clinical course of an individual who has the index disease under study' (Feinstein, 1970). Cardiovascular (CV) morbidity, in particular hypertension, hypercholesterolaemia and ischaemic heart disease (Ahmed et al., 2016, Bremander et al., 2011), is more prevalent in AS than matched controls.

The ASAS-COMorbidities in SPondyloArthropathy (COMOSPA) study is a large multinational multi-centric cross-sectional study outlining in detail the profile of co-morbidities occurring in individuals with SpA (Molto et al., 2016). Eighty-nine percent of individuals in this study fulfilled ASAS classification criteria for axSpA. The most prevalent comorbidities were osteoporosis, affecting 13.4% of the cohort, and gastrointestinal ulceration, affecting 10.7% of the cohort. Almost four percent of the cohort had cardiovascular morbidity. An ancillary analysis of ASAS-COMOSPA suggested that the subtype of SpA, as well as geographical location, likely plays a part in prevalence estimates of cardiovascular disease (Lopez-Medina et al., 2018): prevalence of CV disease was lower in axSpA individuals compared to peripheral SpA individuals; in addition, Mediterranean populations had less cardiovascular disease than Northern European regions. The prevalence of depression was not examined in the ASAS-COMPOSPA study; subsequently Zhao et al explored the prevalence of depression in axSpA in a meta-analysis and reported a pooled prevalence of 15%, with ranges from 11 to 64% (Zhao et al., 2018).

A secondary aim of the ASAS-COMOSPA study (Molto et al., 2016) was to examine whether individuals with axSpA are optimally screened for comorbidities. The authors found that only half of participants had an adequate assessment of their cardiovascular status and optimal cancer screening was performed in 11-44% of participants.

Comorbidities in axSpA add to the burden of disease. The presence of comorbidities in SpA adversely affected physical function, work ability and quality of life in ASAS-COMOSPA (Nikiphorou et al., 2018). Similar findings have been demonstrated by other investigators (Lee et al., 2018, Zhao et al., 2019). Healthcare expenditure is also increased in individuals with comorbidity (Lee et al., 2018).

1.12 Ageing populations

1.12.1 Epidemiology and demographics

The dramatic increase in life expectancy is one of the greatest accomplishments of modern medicine (Arias et al., 2017, European Commission, 2018). In the European Union (EU), life expectancy is expected to increase for men from 78.3 years in 2016 to 86.1 years in 2070 and for women from 83.7 years to 90.3 years in 2070 (European Commission, 2018). In addition, although fertility rates are predicted to increase from 1.58 in 2016 to 1.81 by 2070 across the EU, they are projected to remain less than the natural replacement rate of 2.1 (European Commission, 2018). Together, the outcome of an increase in life expectancy along with the low fertility rates is a projected increase in the proportion of the population aged 65 years and older in the EU relative to those aged 15-64 years, from 29.6% in 2016 to 51.2% by 2070 (European Commission, 2018).

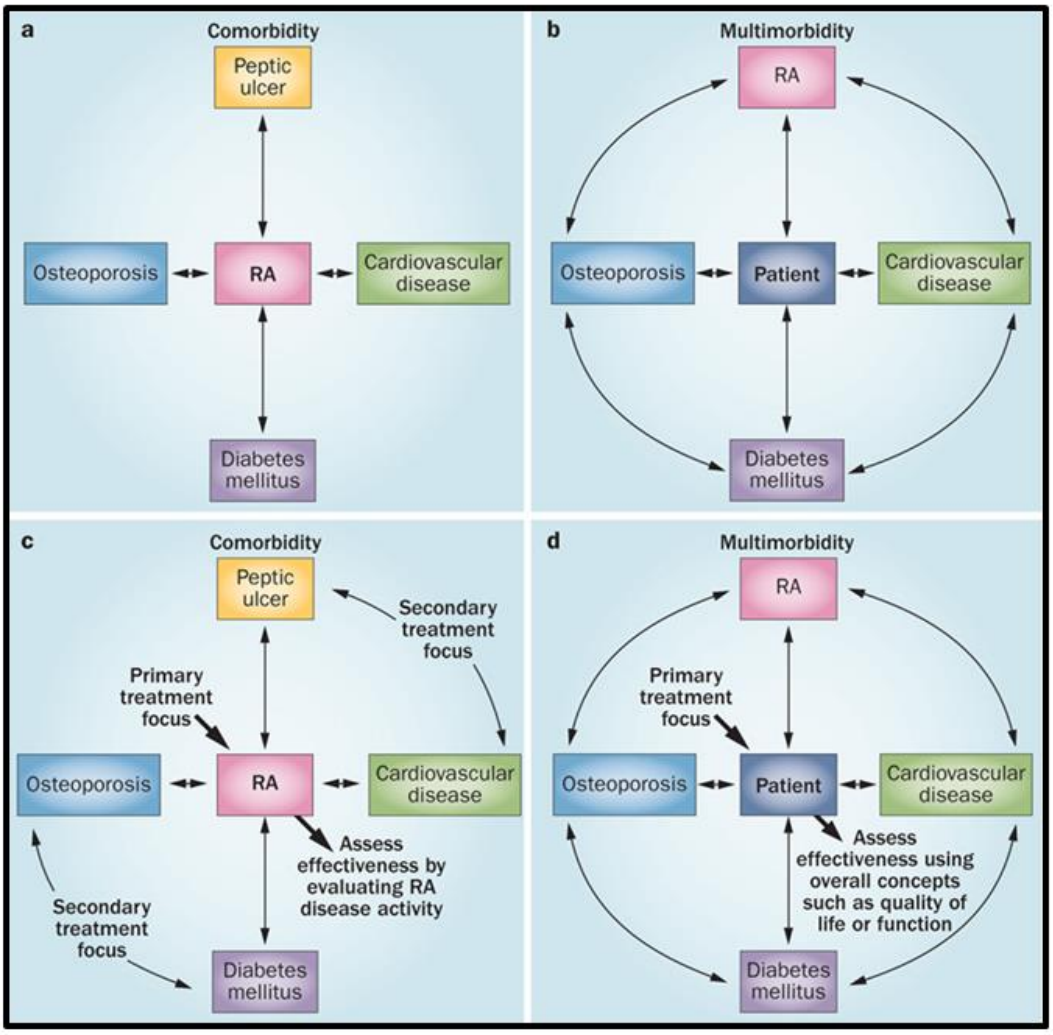
1.12.2 Challenges with ageing populations

Although this population expansion can be considered a great achievement, it is accompanied by many challenges (Rechel et al., 2013, Christensen et al., 2009), including projected increases in age-related expenditure and associated economic burden. A simple aspiration to live longer is no longer the goal. A delayed onset of morbidity and functional decline, termed “compression of morbidity” (Fries, 1983), is now the ambition, where people live longer but with less chronic disease. Unfortunately, this is not the reality and old age is instead accompanied by a greater disease burden. Noncommunicable diseases now represent the biggest threat to mortality worldwide, with deaths projected to increase from 38 million in 2012 to 52 million by the year 2030 (WHO, 2015). In order to cope with the challenges that accompany ageing populations, health systems must adapt (Rechel et al., 2013). Current clinical practise guidelines focus on individual comorbidities, without giving adequate guidance on managing individuals with multiple chronic conditions (Navickas et al., 2016). However, with multiple conditions now becoming the norm, there is increasing pressure to delay the onset of functional decline and facilitate people to remain effective members of society for longer. Therefore, shifting our focus from the isolated management of individual comorbidities to the concept of multimorbidity is suggested (Navickas et al., 2016).

1.12.3 Multimorbidity

Although the definition can vary, multimorbidity is widely accepted as the presence of two or more chronic conditions in the one individual, without specifying the index disease (Almirall and Fortin, 2013). In contrast, a comorbidity can be defined as "any distinct additional clinical entity that has existed or that may occur during the clinical course of an individual who has the index disease under study" (Feinstein, 1970). Considering multimorbidity when managing patients shifts our focus from a narrow view of considering each condition in isolation to a more holistic approach, whereby the individual is considered as the centre of care and all aspects of their condition are considered together (Navickas et al., 2016, Radner et al., 2014) (see Figure 1-11).

Figure 1-11: Comorbidity and multimorbidity in rheumatic disease, with rheumatoid arthritis as the index disease for example purposes (Radner et al., 2014). (a) For comorbidity, RA is the index disease and all other diseases are regarded consequential. (b) In multimorbidity, the patient is of central concern and all diseases are of equal importance with interactions between each other. (c) In comorbidity treatment is primarily focused on the index disease and the effect quantified by evaluating RA disease activity. (d) In the multimorbidity concept treatment focuses on the patient and treatment effectiveness is quantified by overall indicators such as quality of life or physical function. RA, rheumatoid arthritis.



Multimorbidity estimates in the general population range from 13-95%, with prevalence increasing with age (Violan et al., 2014, Barnett et al., 2012). Multimorbid individuals have increased mortality, more disability, worse quality of life and greater utilisation of healthcare resources (Menotti et al., 2001, McDaid et al., 2013, Cassell et al., 2018); in some cases, 25% of the population accounts for more than 50% of health utilisation (Cassell et al., 2018). Musculoskeletal disease (MSD) is commonly found in individuals with multimorbidity (Simoes et al., 2017) and its presence serves to intensify the impact (van der Zee-Neuen et al., 2016, Duffield et al., 2017).

1.12.4 Multimorbidity in rheumatic diseases

In rheumatoid arthritis, 62-65% of individuals are multimorbid i.e. at least one additional co-morbid conditions in addition to RA (Radner et al., 2015b, Radner et al., 2015c). The mean number of comorbid conditions is 2.6 (Radner et al., 2015c) in individuals with RA. RA patients with increasing multimorbidity have worse physical function also (Radner et al., 2014) and have lower rates of remission or low disease activity achievement (Radner et al., 2015a). Multimorbid RA patients are also less likely to be treated with biological DMARDs (Radner et al., 2015b). Individuals with RA in general are often undertreated for co-morbidities – for example statins are known to reduce CV risk in RA patients (Danninger et al., 2014), yet they are often underutilised (Toms et al., 2010). To date, multimorbidity has not been explored in axSpA.

1.13 Osteoporosis

Much of this thesis will discuss osteoporosis in the context of axSpA. This subsequent section aims to introduce the general topic of osteoporosis to the reader.

1.14 Relevant definitions

1.14.1 World Health Organisation definition

Osteoporosis was defined in 1993 by international consensus as a systemic skeletal disease, which is characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (1993). In 1994, an operational definition of osteoporosis was released by the World Health Organisation (WHO), in a report detailing the assessment of fracture risk and its application to screening for postmenopausal osteoporosis (1994). In the WHO definition, bone mineral density (BMD) is compared to the BMD of a healthy young woman, with osteoporosis defined as a T score of less than or equal to -2.5 and osteopenia (low BMD) is defined as a T score between -1 and -2.5 (1994). In 2008, the WHO refined the definition with the femoral neck as the standard measurement site and white females aged 20-29 years in the National Health and Nutrition Examination Survey (NHANES) III reference database as the recommended reference range (Kanis et al., 2008).

1.14.2 International Society of Clinical Densitometry definition

The International Society of Clinical Densitometry (ISCD) adopted this definition and define osteoporosis as a T-score of -2.5 or less at the femoral neck, lumbar spine or total hip in postmenopausal women and men age 50 years or older (Shepherd et al., 2015). The ISCD also recommends the NHANES III database as the reference standard used to calculate T-scores for the hip and manufacturers own database for the spine (Shepherd et al., 2015). Z scores are preferred for pre-menopausal women and men under the age of 50 years, with a Z score of -2.0 or lower considered ‘below the expected range for age’ and a Z score above -2.0 ‘within the expected range for age’ (Shepherd et al., 2015).

1.14.3 Osteoporotic fracture definition

The clinical significance of osteoporosis is in its increased susceptibility to fractures. The majority of low-trauma fractures, that is, fractures which occur as a result of a fall from a standing height or less, are considered osteoporotic (Seeley et al., 1991, Stone et al., 2003, Center et al., 2007). A fragility fracture is defined by the WHO as a fracture which is caused by an injury that

would be insufficient to fracture a normal bone (World Health Organization, 1998) and is usually associated with low BMD and increased risk of future fractures (Melton et al., 1997). However, individuals with osteoporosis are more likely than their counterparts with normal BMD to fracture at any trauma level (Mackey et al., 2007). Individuals with osteoporosis by dual-energy x-ray absorptiometry (DXA) are at the highest risk of sustaining a fragility fracture; however, the prevalence of fragility fractures is highest in those with low bone mass rather than osteoporosis, as there are more individuals with bone mass in this range than with overt osteoporosis (Pasco et al., 2006, Szulc et al., 2005).

Other components such as the micro-architecture of bone contribute to the risk of fracture as well, not merely bone mass (Hernlund et al., 2013). The most common sites for fragility fractures are hip, vertebra and wrist (Cosman et al., 2014).

1.15 Assessment of BMD

1.15.1 Dual-energy x-ray absorptiometry (DXA)

DXA is the current gold standard recommended by the ISCD to assess BMD in clinical practice (Shepherd et al., 2015). It uses two x-ray beams with differing peak voltage, allowing it to subtract the soft tissue component (Link, 2012). It is used to assess BMD of the lumbar spine, proximal femur and radius. It provides a measure of BMD in grams per centimetre-squared, as well as T- and Z-scores. BMD as measured by DXA correlates well with bone strength, explaining approximately 70% of the variation (1993). It has some disadvantages (Link, 2012): it is a two-dimensional picture of a three-dimensional structure, therefore does not give an estimate of the volumetric density; it contains ionising radiation, albeit small doses; it is sensitive to artefact, in particular degenerative change; in obese individuals, superimposed soft tissue will increase BMD due to the attenuation of the x-ray beams and beam hardening artefact. In addition, the presence of aortic calcifications can affect measurements of BMD of the spine (Link, 2012), an issue known to affect 22% of an AS population (Rueda-Gotor et al., 2018).

1.15.2 Quantitative computed tomography (qCT)

QCT is another technique which can be used to assess BMD, primarily of the lumbar spine (L1-3). Density is measured in Hounsfield units, which are converted to BMD measured in milligrams hydroxyapatite per cubic centimetre. Some advantages of qCT include the ability to provide volumetric measurements of the lumbar spine, which are independent of body size (Link, 2012); it assesses trabecular bone, which is more sensitive for the monitoring of change (Black et al.,

2003); it can predict fragility fractures (Yu et al., 1995). A major disadvantage is that qCT has a higher radiation dose, prohibiting its routine use in clinical care.

1.15.3 Trabecular bone score (TBS)

TBS is a novel technique which can be applied to DXA images by quantifying local variations in grey level (Hans et al., 2011a). It uses experimental variograms of two-dimensional projection images, quantifying variation in grey-level texture from one pixel to the next, allowing the differentiation between three-dimensional microarchitecture that has the same BMD but different trabecular characteristics (Hans et al., 2011b, Hans et al., 2011a). Higher TBS scores reflect stronger bone, which is more fracture-resistant (Pothuaud et al., 2009, Hans et al., 2011a). TBS can be applied retrospectively to DXA images. TBS has been shown to predict fractures, both in combination with DXA and independently (Rabier et al., 2010, Winzenrieth et al., 2010, Leslie et al., 2009, Hans et al., 2011b).

1.16 Epidemiology of osteoporosis

1.16.1 Global prevalence

Osteoporosis is an important non-communicable disease. In the Global Burden of Disease study, osteoporotic fractures were an important part of musculoskeletal conditions, which were a leading cause of disability (GBD 2013 DALYs and HALE Collaborators, 2018). Osteoporosis is predominantly a disease of the elderly population: fragility fractures are rare before the age of 50 years and the incidence increases progressively thereafter. It is estimated that at 50 years of age, a white woman has a 15-20% lifetime risk of hip fracture and a 50% risk of any osteoporotic fracture (Cummings et al., 1989, Cummings and Melton, 2002). An estimated 22 million women and 5.5 million men had osteoporosis using WHO criteria in the EU in 2010, with an approximate prevalence of 6.6% in men and 22.1% in women over the age of 50 years (Hernlund et al., 2013). The number of new fractures in the same year was estimated to be 3.5 million:

- Hip: 620,000
- Vertebral: 520,000
- Forearm: 560,000
- Other: 1.8 million.

With the projected population expansion, the prevalence of osteoporosis is expected to increase in the coming years, with an increase of 23% predicted by 2025 (Hernlund et al., 2013).

1.16.2 Economic burden

The economic cost associated with osteoporosis is high. The direct cost of osteoporosis in Ireland in 2010 was estimated at €223 million (Svedbom et al., 2013). In addition, the estimated number of quality adjusted life years (QALYs) lost as a result of osteoporosis was 6,100 in 2010 at an estimated cost of €430 million, with the majority of loss (68%) occurring in women (Svedbom et al., 2013). When the cost of osteoporosis is considered along with value of the QALYs lost (estimated at 2 x gross domestic product (GDP)), the total cost of osteoporosis in Ireland in 2010 was estimated at €650 million. As the population over the age of 50 years is estimated to increase by 42% by 2025, the costs associated with osteoporosis in Ireland are predicted to also increase, estimated to reach approximately €890 million (Svedbom et al., 2013).

1.16.3 Fracture sites

1.16.3.1 Hip fractures

The incidence of hip fractures in Ireland was 140 (men) and 407 (women) per 100,000 years between 2000 and 2004, with hip fracture numbers estimated to increase by 100% by the year 2026 (Dodds et al., 2009). Hip fractures present with pain and inability to weight bear and almost always requires surgical fixation (Compston et al., 2019). Hip fractures are associated with an excess mortality, both short- and long-term (Katsoulis et al., 2017, von Friesendorff et al., 2016), with approximately half of all fracture-related deaths in women due to hip fractures (Hernlund et al., 2013). A systematic review in 2008 demonstrated an excess mortality in the first year after a hip fracture ranging from 8.4% to 36% (Abrahamsen et al., 2009). Although the risk of death was highest in the days and weeks after the fracture, risk remained elevated for months to years afterwards. Similar findings were seen in another meta-analysis, where older adults have a five- to eight-times increased risk of mortality during the first three months after a hip fracture (Haentjens et al., 2010).

A hip fracture has a significant impact on an older person's ability and function, with the majority of affected individuals not returning to their pre-fracture health status and quality of life (Peeters et al., 2016). Approximately half of hip fracture patients recover their pre-fracture level of mobility and function, up to 20% are institutionalised and the remainder require assistance with tasks at one- and two-years post fracture (Dyer et al., 2016). Reduced physical function, loss of independence and chronic pain are common (Sanchez-Riera and Wilson, 2017).

1.16.3.2 Vertebral fractures

Vertebral fractures have a wide range of presentations, varying from an incidental pick-up on a plain film to hospital admission secondary to severe pain (Schousboe, 2016, Ensrud et al., 2016, Fink et al., 2005). However, even if a vertebral fracture is clinically asymptomatic, they have importance in highlighting an increased risk of future fracture, particularly hip fracture, and so can be considered as a marker of skeletal fragility (Compston et al., 2019, Naves et al., 2003).

Vertebral fractures are associated with excess mortality (Jalava et al., 2003), as well as significant morbidity (Svedbom et al., 2018, Al-Sari et al., 2016). Twenty-eight percent of fracture-related deaths are due to vertebral fractures (Hernlund et al., 2013). Outcomes after clinically evident vertebral fractures are particularly poor, with an in-hospital mortality of up to 35% and a one-year mortality of 20% to 27%, along with high levels of disability in survivors (Ong et al., 2018).

1.16.3.3 Non-vertebral non-hip fractures

Fractures outside the hip and vertebrae account for 90% of all fractures in individuals up to the age of 80 years, and for 59% of fractures in older individuals (Hagino, 2013). Forearm fractures are a particularly common site of osteoporotic fractures, accounting for 16% of all osteoporotic fractures in Europe in 2010 (Hernlund et al., 2013). The annual incidence of osteoporosis-related forearm fractures is estimated at 2.68/1,000 population aged 40 to 75 years in Northern Ireland (Beringer et al., 2005). Osteoporosis of the forearm is associated with an increased risk of death (Hauger et al., 2018). Forearm fractures also increase the risk for future fragility factures, particularly of the hip (Daruwalla et al., 2016, Hansen et al., 2015).

1.17 Normal bone physiology

Bone consists of type 1 collagen, stiffened by crystals of calcium hydroxyapatite (Seeman and Delmas, 2006). There are two components of bone: outer cortical bone and inner trabecular bone (Cooper et al., 2016). The proportions of cortical and trabecular bone vary according to the skeletal site: trabecular bone predominates in the vertebrae, whereas long bones contain mainly cortical bone (Compston et al., 2019).

During life, bone undergoes modelling and remodelling to grow or change shape (Katsimbri, 2017). During childhood, modelling is the predominant process in children, with bones growing in length and width, optimising the shape and structure of the bone to respond to prevailing mechanical stresses (Frost, 1990a).

In adulthood, remodelling predominates, where old bone is replaced by new bone. Bone is a dynamic organ: the skeleton is renewed approximately every ten years (Compston et al., 2019). The remodelling process uses two major cell types: osteoblasts to form bone and osteoclasts to resorb bone (Frost, 1969). Osteoblasts and osteoclasts form the bone multicellular unit (MCU), which is responsible for remodelling and occurs at discrete sites (Hattner et al., 1965). This process is usually very tightly regulated, with bone resorption and bone formation occurring in sequence (coupled), and thus the bone mass remains constant (Hattner et al., 1965, Frost, 1990b). Remodelling allows bone to adapt to biomechanical influences, repairing damage and maintaining calcium levels as needed (Goldring, 2013).

There are 3 major types of bone cells:

1. **Osteoblasts**

Osteoblasts are bone-forming cells, responsible for making and mineralising the skeleton. They develop from the differentiation of mesenchymal progenitor cells. This process of differentiation is stimulated by activation of runt-related transcription factor 2 (RUNX2), which is expressed on the mesenchymal progenitor cells (Gaur et al., 2005, Lian et al., 2006). RUNX2 is activated through the interaction of bone morphogenetic proteins (BMPs) with their receptors, causing phosphorylation of Smad proteins. Transforming growth factor-ß (TGF-ß), parathyroid hormone (PTH) and fibroblast growth factor also affect RUNX2, and therefore osteoblastogenesis (Redlich and Smolen, 2012).

The Wnt-Frizzled-ß-catenin signalling pathway is also important in the differentiation and activation of osteoblasts (Yamada et al., 2013, Redlich and Smolen, 2012, Bodine and Komm, 2006). Wnt proteins bind to the Frizzled receptor and associated low-density lipoprotein receptor-related proteins (LRPs), then signal via ß-catenin (Bodine and Komm, 2006). Dickkopf-related protein 1 (DKK1) can inhibit the Wnt pathway by binding to the LRPs, thus preventing the LRPs from binding with Wnt (Mao et al., 2002). Sclerostin can also inhibit the activation of osteoclasts by binding to LRPs (in slightly different manner to DKK1), thus inhibiting the Wnt pathway (ten Dijke et al., 2008, Moester et al., 2010). PTH also utilises the ß-catenin pathway to activate osteoblasts. These pathways are summarised in Figure 1-12.

Osteoblasts express receptor activator of nuclear factor-κß ligand (RANKL), important in the differentiation of osteoclasts. Osteoblasts can also produce osteoprotegerin (OPG), which binds to RANKL and inhibits osteoclast activation, thus protecting against bone loss (Redlich and Smolen, 2012).

Osteoblast activation leads to the production of matrix proteins, including type 1 collagen which forms the major bone matrix protein (Katsimbri, 2017). Osteoblasts also aid in the mineralisation of the osteoid: hydroxyapatite crystals form through the combining of phosphates released from osteoblast-derived matrix vesicles in the osteoid and calcium from the extracellular fluid (Katsimbri, 2017). Osteoblast activation additionally produces regulators of matrix mineralisation such as osteopontin and osteonectin (Redlich and Smolen, 2012).

2. Osteocytes

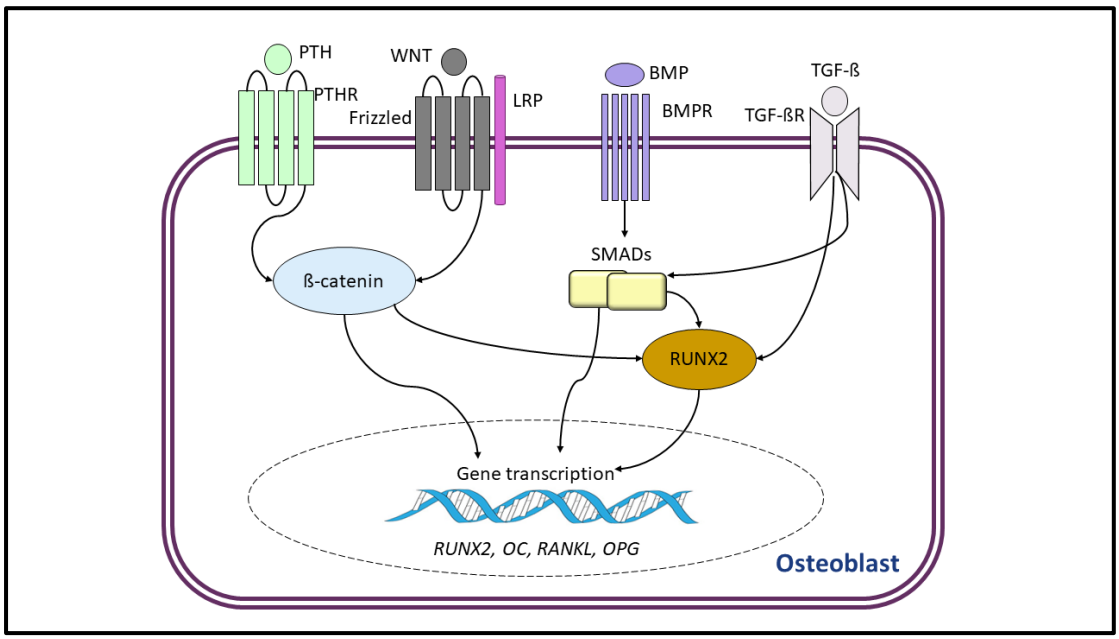
Mature osteoblasts predominantly develop into osteocytes, although some become lining cells covering bone surfaces. Osteocytes are the most abundant bone cell population. They used to be considered inert cells; however, they are now known to produce several molecules; they are thought to have a role in mechanosensing and mechanotransduction, thus fulfilling an important role in the regulation of bone remodelling, as well as influencing both osteoblast and osteoclast function (Redlich and Smolen, 2012, Okamoto et al., 2017).

3. Osteoclasts

Osteoclasts are responsible for bone resorption. They are derived from haematopoietic stem cells. Macrophage colony-stimulating factor (M-CSF), along with its receptor FMS are required for the proliferation and activation of osteoclasts (Redlich and Smolen, 2012). Binding of RANKL, which is expressed on the surface of osteoblasts, to RANK is also essential for activating osteoclasts. Although osteoblasts are the major source of RANKL expression, other cells can also express this, including activated T-lymphocytes, which are implicated in inducing bone loss. Micro-ribonucleic acid molecules (miRNAs) are also involved in regulating osteoclastogenesis. They have a role in regulating cell differentiation, proliferation and death, including osteoclast differentiation and function.

Osteoclasts are located on the cell surface and bone resorption is mediated through matrix-degrading enzymes such as cathepsin K and the matrix metalloproteinases (MMP) (Okamoto et al., 2017).

Figure 1-12: Simplified summary of key pathways involved in osteoblast signalling during health. Adapted from (Redlich and Smolen, 2012). BMP: bone morphogenetic protein; BMPR: bone morphogenetic protein receptor; LRP: low-density lipoprotein; OC: osteocalcin; OPG: osteoprotegerin; PTH: parathyroid hormone; PTHR: parathyroid hormone receptor; RANKL: Receptor activator of nuclear factor-κß ligand; RUNX: runt-related transcription factor; TGF: transforming growth factor; TGFR: transforming growth factor receptor.

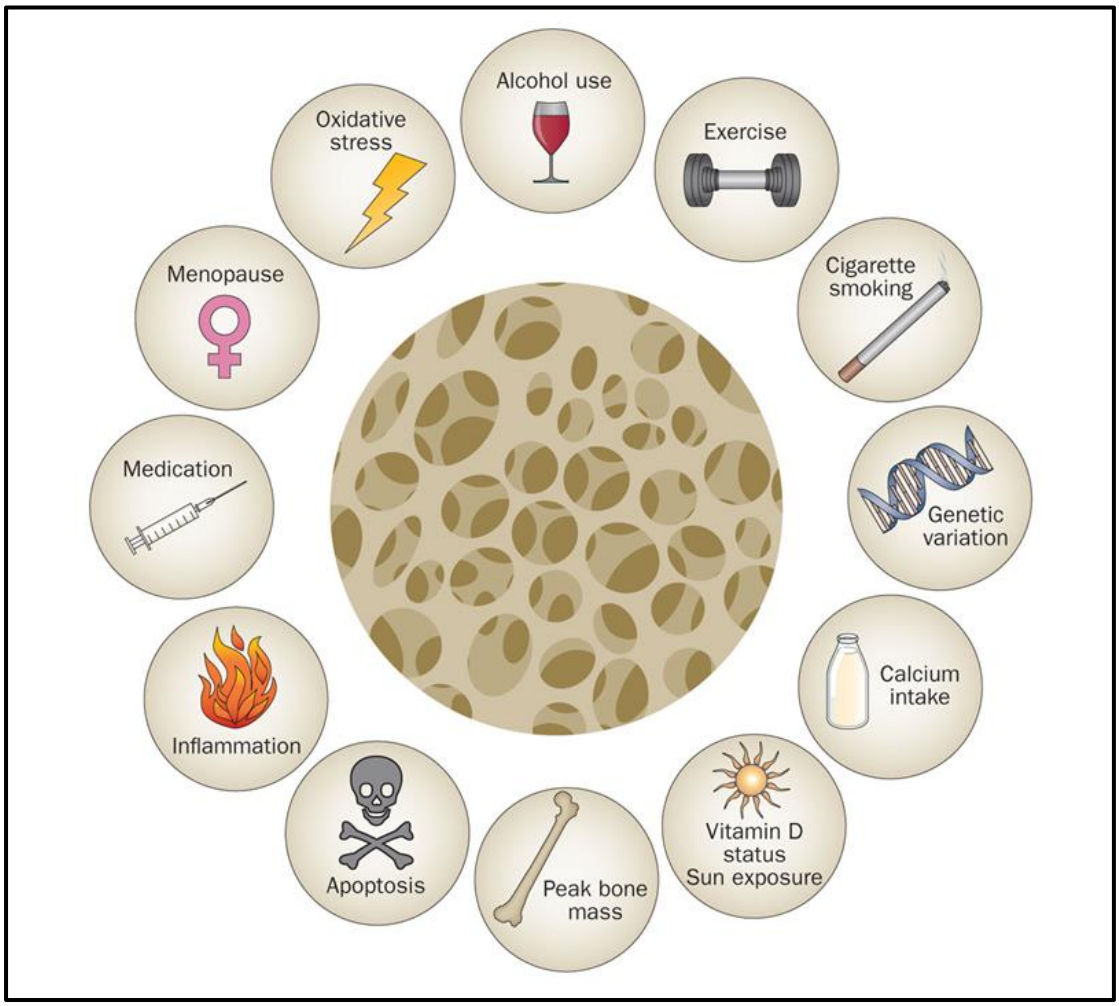


1.18 Pathophysiology of osteoporosis

Osteoporosis translates literally to ‘porous bone’. Both males and females begin to experience a decline in their BMD once peak bone mass is reached (Hendrickx et al., 2015). If bone formation in the MCU is less than the resorption, for example with oestrogen deficiency, each episode of remodelling will lead to the removal of bone from the skeleton, resulting in bone loss, or osteoporosis (Seeman and Delmas, 2006). In trabecular bone, trabecular thinning and loss of trabeculae is seen (Parfitt et al., 1983); reduced cortical thickness and increased porosity occurs due to a combination of endocortical and intracortical bone loss (Zebaze et al., 2010).

There are several mechanisms which can contribute to an individual’s likelihood of developing osteoporosis, including oxidative stress, apoptotic mechanisms, sex-steroid deficiency and macroautophagy (Hendrickx et al., 2015). Sex steroids are particularly important in maintaining the balance between bone formation and bone resorption (Seeman, 2002). The loss of oestrogen in women with age leads to an accelerated loss of BMD, due to a prolonged lifespan of osteoclasts and decreased lifespan of osteoblasts and osteocytes (Manolagas, 2010). Lifestyle factors are also important, with diet, physical activity, smoking and alcohol consumption all having considerable effects on an individual’s susceptibility to osteoporotic fracture (see Figure 1-13) (Hendrickx et al., 2015).

Figure 1-13: Factors that influence the development of osteoporosis (Hendrickx et al., 2015).



1.18.1 Bone turnover markers

Bone turnover markers (BTMs) are products released by bone proteins or bone cells during the bone formation and resorption process (Morris et al., 2017). They can be measured in blood or urine, making them an attractive technique to assess bone turnover: currently, bone histomorphometry via bone biopsy is the gold standard to assess bone turnover, but it is not a practical technique for clinical use due to its invasive nature and the need for specialist laboratory interpretation (Eastell et al., 2018). BTMs have been validated against gold standard methods for measuring bone turnover (Eastell et al., 2018).

Much research has been performed looking at the role of bone turnover markers (BTMs) in osteoporosis in the general population. Although they have not been shown to have a clinically useful role in predicting future bone loss in postmenopausal women (Greenblatt et al., 2017), high levels of BTMs have been shown to predict future fragility fractures in the general population

(Greenblatt et al., 2017, Johansson et al., 2014, Tian et al., 2019). BTMs also have a role in monitoring response to treatment (Morris et al., 2017).

BTMS can be divided into bone resorption markers and bone formation markers. Bone formation markers include osteocalcin, N-propeptide of type 1 collagen (P1NP) and the bone isoform of alkaline phosphatase (ALP) (Eastell et al., 2018). Osteocalcin is secreted by osteoblasts and is the most abundant non-collagen protein in bone (Greenblatt et al., 2017). P1NP is cleaved from type 1 pro-collagen during extracellular processing, when it is assembled into fibrils (Szulc et al., 2017). Bone resorption markers include C-terminal telopeptides of type 1 collagen (CTX-I), which contains pyridinium cross-links and is formed when the telopeptides of type 1 collagen are cleaved as the osteoclasts resorb bone and are released into the circulation, where the level can be measured (Greenblatt et al., 2017). The International Osteoporosis Foundation and International Federation of Clinical Chemistry have recommended serum P1NP and CTX as the reference BTMs (Vasikaran et al., 2011).

CTX-I exhibits a circadian pattern, peaking in the early hours of the morning and dropping to its lowest by early afternoon. Food intake also affects CTX-I levels. Therefore, it is recommended that BTMs are taken following an overnight fast, ideally between 7.30am and 10am. They should be centrifuged within two hours and stored at -20^{o}C until analysis (Szulc et al., 2017).

1.18.2 Vitamin D

Vitamin D is a hormone which is required for the maintenance of calcium levels in the blood and for healthy mineralisation of bone (Essouma and Noubiap, 2017). Conflicting results have been reported regarding the link between vitamin D deficiency and fracture risk, but overall the evidence does appear to support the use of vitamin D to reduce the risk of fractures (Brincat et al., 2015). However, the importance of vitamin D goes beyond bone, with the discovery of receptors for vitamin D in almost every tissue and cell in the body (Brincat et al., 2015). Indeed, a meta-analysis with over 26,000 participants demonstrated an association between vitamin D levels and all-cause and cause-specific mortality (Schottker et al., 2014).

1.19 Management of osteoporosis

1.19.1 Lifestyle measures

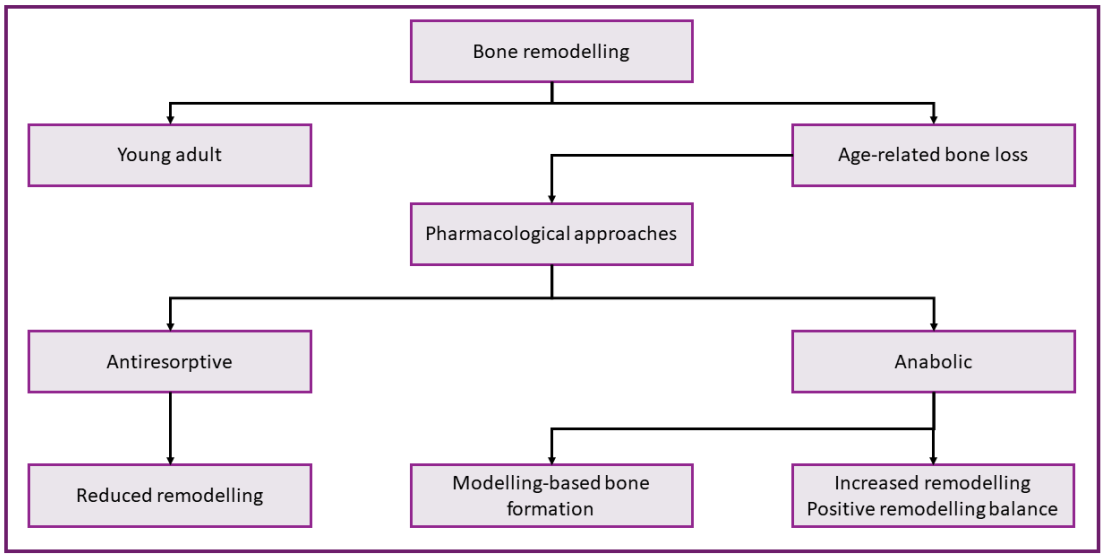
When considering the utility of treating osteoporosis, it is important to understand that the primary aim is to reduce the risk of fragility fractures, therefore improving BMD and reducing fall frequency are both beneficial. General lifestyle measures such as good nutrition, regular physical activity, stopping smoking, are all recommended for individuals with and at risk of osteoporosis (Cosman et al., 2014, Compston et al., 2019, Camacho et al., 2016). Calcium and vitamin D supplementation appear to have little benefit in individuals who are already replete, but correction of deficiencies can be beneficial (Compston et al., 2019, Cauley et al., 2013, Jackson and Shidham, 2007). Excessive intake of calcium has been associated with renal stone and cardiovascular disease, although this latter relationship is less certain (Jackson et al., 2006, Bolland et al., 2011).

Fall prevention programmes are effective in reducing falls frequency, but efficacy in reducing fracture risk hasn't been shown (Gillespie et al., 2012, Hopewell et al., 2018). Exercise interventions have a small but statistically significant effect on BMD, but no effect on risk of fractures (Howe et al., 2011, Hagen et al., 2012).

1.19.2 Bisphosphonates

Bisphosphonates are a class of pharmacological drugs known to be effective in treating osteoporosis. Bisphosphonates are potent antiresorptive medications (see Figure 1-14), exerting their pharmacological effect by inhibiting bone resorption by osteoclasts, thus decreasing bone turnover (Eriksen et al., 2014). Alendronate, risedronate and zoledronic acid all reduce the risk of vertebral, non-vertebral and hip fractures (Black et al., 2000, Black et al., 2007, Reginster et al., 2000, Harris et al., 1999, Cummings et al., 1998, Black et al., 1996, Black et al., 2006, Eriksen et al., 2014). Ibandronate has been shown to reduce vertebral fracture risk, but its efficacy on non-vertebral and hip fractures is less certain (Barrionuevo et al., 2019). With prolonged therapy, atypical femoral fractures (subtrochanteric or femoral shaft) can occur (Shane et al., 2014) and a drug holiday of two to three years should be considered in individuals on bisphosphonates for five years but not at high risk of fracture (Shane et al., 2014, Anagnostis et al., 2017).

Figure 1-14: Effects of antiresorptive and anabolic pharmacological treatments on bone remodelling and modelling (Compston et al., 2019).



1.19.3 RANK ligand inhibitor

Denosumab is a fully human monoclonal antibody against RANKL (receptor activator of nuclear factor-kappaB ligand), preventing the interaction of RANKL with its receptor RANK, thus reversibly inhibiting osteoclast-mediated bone resorption. It can also improve cortical bone structure at several sites, including the hip, which leads to an increase in cortical thickness and decrease in porosity (Compston et al., 2019). It is administered by subcutaneous injection every six months. It has been shown to reduce vertebral, non-vertebral and hip fractures, with results evidence within the first year of treatment (Cummings et al., 2009). It has comparable efficacy to bisphosphonates in reducing fractures and superior efficacy in increasing BMD (Beaudoin et al., 2016), with consistent increase in BMD seen over ten years of treatment (Bone et al., 2017).

In contrast to bisphosphonates, if denosumab is stopped bone remodelling increases rapidly, BMD decreases, and the loss of vertebral fracture protection is seen, with multiple vertebral fractures seen three to 18 months after stopping treatment (Cummings et al., 2018). Consideration should be given to commencing bisphosphonate therapy if denosumab is withdrawn (Tsourdi et al., 2017).

1.19.4 Teriparatide

Teriparatide is an anabolic agent, which increases formation of bone through changes in bone remodelling, bone modelling or a combination of the two (see Figure 1-14). It is administered by

subcutaneous injection daily for 18 to 24 months. It has been shown to be effective in increasing BMD of the spine and reduces the risk of vertebral and non-vertebral fractures (Neer et al., 2001, Wang et al., 2017). Use of teriparatide is limited to 24 months, due to concerns regarding osteosarcoma, a theoretical rather than proven concern, but post-marketing surveillance is ongoing due to the rarity of this cancer (Andrews et al., 2012, Gilsenan et al., 2018). Once teriparatide is discontinued, switching to denosumab or bisphosphonate will preserve BMD (Compston et al., 2019).

1.19.5 Other pharmacological treatments

Oestrogen therapy can prevent bone loss in postmenopausal women and reduce the risk of fractures by 34% (Cauley et al., 2003), but shouldn't be continued more than ten years post menopause due to cardiovascular concerns (Compston et al., 2019). Abaloparatide is a synthetic analogue of parathyroid-related peptide and has similar effects to teriparatide (Miller et al., 2016). It is currently licenced in the US, but not in Europe due to concerns regarding cardiovascular risks. Romosozumab is a humanised antibody that binds sclerostin, thus activating bone formation and reducing bone resorption. It has been shown to be more effective than treatment with denosumab or alendronate (Cosman et al., 2016, Saag et al., 2017). It was approved in April by the Federal Drugs Agency (FDA) for use in the US but has recently been rejected by the European Medicines Agency due to concerns regarding cardiovascular health.

1.20 Thesis aims and objectives

The aim of this thesis is to comprehensively examine osteoporosis in adults with axSpA. In order to achieve this aim, a number of studies were completed. See Figure 1-15 for a schematic outlining the aims and objectives of the thesis.

In Section 1.11.2, the burden of comorbidity in individuals with axSpA was outlined. In the multinational ASAS-COMOSPA study, osteoporosis was the most prevalent comorbidity. Ireland was not included in this study, therefore the prevalence of osteoporosis in adults with axSpA in Ireland has never been examined. In addition, multimorbidity has never been examined in a cohort of people with axSpA. The aim of Study 1 was to examine the burden of comorbidity in adults with axSpA in Ireland using data from a large national cross-sectional registry, with the specific objectives of (1) defining the profile of comorbid conditions in axSpA, (2) assessing the prevalence of multimorbidity, (3) examining the association between multimorbidity and disease outcomes, and (4) assessing the prevalence of osteoporosis in axSpA in Ireland. The results are presented in Chapter 2.

The finding of a high prevalence of osteoporosis amongst Irish adults with axSpA led to a comprehensive narrative literature review exploring measurement techniques, epidemiology and risk factors for osteoporosis in axSpA, presented in Chapter 3.

Consideration of the gaps identified in the literature formed the basis of a large cross-sectional study of individuals with axSpA, with three parts.

One identified gap was the inadequacy of conventional DXA when assessing BMD of the spine in axSpA. Thus, Study 2 was designed, a cross-sectional study with the primary aim of comparing lateral and conventional DXA in their ability to assess BMD of the spine. Secondary aims included (1) assessing the prevalence of osteoporosis and vertebral fractures in adults with axSpA, and (2) exploring associations with low BMD. This study is described in Chapter 4.

Study 3 was conducted to investigate associations between serum biomarkers and osteoporosis in individuals with axSpA, as this is currently unknown in the literature. The results are outlined in Chapter 5.

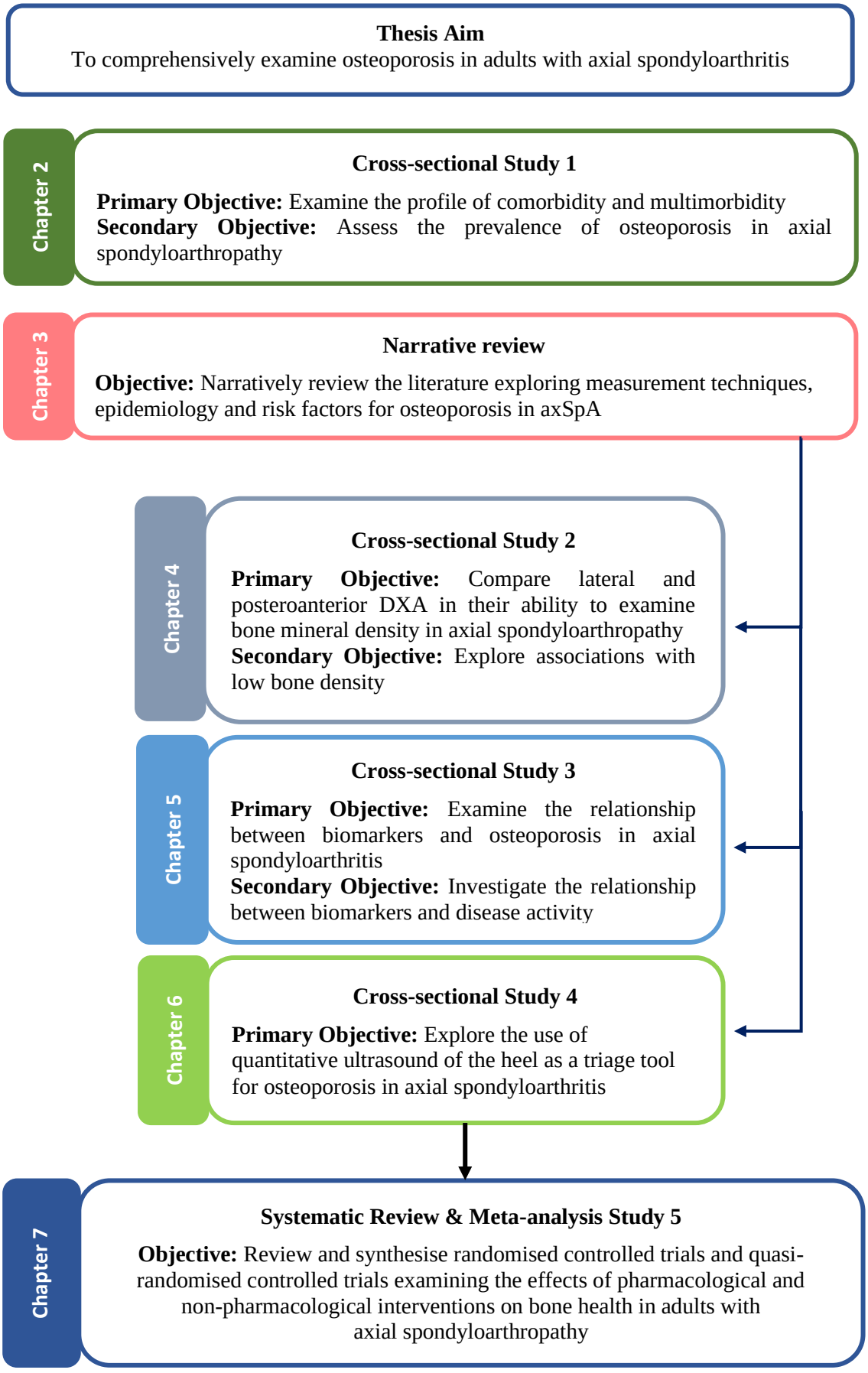
Due to limited resources in an increasingly ageing population, access to DXA can be reduced, with the potential for a delay in diagnosing low BMD. Study 4, presented in Chapter 6, aimed to explore the use of quantitative ultrasound (QUS) of the calcaneus as a triage tool for osteoporosis

in individuals with axSpA. A secondary aim was to assess the ability of QUS to reduce the need for DXA assessment.

Having firmly established that osteoporosis is a prevalent condition, the final study aimed to review and synthesise randomised controlled trials (RCTs) and quasi(q)-RCTS examining the effects of pharmacological and non-pharmacological interventions on bone health in individuals with axSpA. The results of the systematic review and meta-analysis are presented in Chapter 7.

Finally, Chapter 8 summarised the overall findings of the thesis, the implications for clinical practice and areas for future research.

Figure 1-15: Overview of aims and objectives of thesis.



Chapter 2 Cross-sectional analysis of comorbidities in axial spondyloarthropathy: results from the Ankylosing Spondylitis Registry of Ireland (ASRI)

Material from this chapter has been disseminated in the following publication:

> Fitzgerald G, Gallagher P, O' Shea F. (2020) Multimorbidity is common in axial spondyloarthropathy and is associated with worse disease outcomes: results from the ASRI cohort. *Journal of Rheumatology*. Feb;47(2):218-226. Epub 2019 May 15.

(full manuscript in Appendix A).

2.1 Introduction

Comorbidity is prevalent in axSpA and is associated with an increased burden of disease (Section 1.11.2). In a world with an ageing population, increasing emphasis is being placed on the compression of morbidity (Fries, 1983). The literature supports a shift in focus from solely examining individual comorbidities to also considering multimorbidity (Navickas et al., 2016). These two concepts are not mutually exclusive, but rather multimorbidity represents a broader more holistic concept than comorbidity alone.

The ASAS-COMOSPA study (Molto et al., 2016) described the occurrence of individual comorbidities in individuals with axSpA, identifying osteoporosis as the most prevalent comorbidity (Section 1.11.2). The presence of comorbidity was also associated with an increased burden of disease (Nikiphorou et al., 2018). However, this study did not include patients from Ireland, therefore the profile of comorbidities in axSpA patients in Ireland is unknown. In particular, whether osteoporosis is as frequent as demonstrated in COMOSPA is unknown. In addition, multimorbidity is known to be prevalent in other rheumatic conditions (Section 1.12.4), but it has not been examined in axSpA to date.

These gaps in the literature represent unmet needs in axSpA. Considering that much of the excess morbidity and mortality that occurs in axSpA is due to comorbid conditions, furthering our knowledge of multimorbidity and the profile of comorbid conditions is needed.

Therefore, the aim of this study was to examine the burden of comorbidity in axSpA patients in Ireland using a large cross-sectional national registry. The specific objectives were to:

1. Define the profile of comorbid conditions in axSpA
2. Assess the prevalence of multimorbidity in adults with axSpA
3. Examine the association between multimorbidity and disease outcomes
4. Assess the prevalence of osteoporosis in axSpA patients in Ireland and compare to internationally reported figures.

2.2 Methods

2.2.1 Ankylosing Spondylitis Registry of Ireland (ASRI)

2.2.1.1 Background

This study was conducted within the framework of the Ankylosing Spondylitis Registry of Ireland (ASRI) cohort. ASRI was established in 2013. It is a large observational cross-sectional multicentre cohort study, which is ongoing. The overarching aim of ASRI is to measure the burden of axSpA disease in the Irish population, through comprehensively assessing as much of the Irish axSpA population as possible. Using this information, it is hoped that ASRI will be able to identify predictors of poor disease outcome.

2.2.1.2 Inclusion criteria

All hospitals in Ireland with a Consultant Rheumatologist are invited to recruit patients to ASRI. To date, twelve centres in Ireland have recruited patients and contributed data to ASRI. Within each participating centre, consecutive patients are invited to partake in ASRI if they have a clinical diagnosis of axSpA, made by a Rheumatologist, and have attended secondary or tertiary care in the preceding three years. Patients are excluded if they have cognitive or other impairment which prohibits them from providing informed consent.

2.2.1.3 Governance

The primary investigator of ASRI (FOS) has responsibility for overall oversight of the ASRI database. Each participating centre has a designated sub-investigator, who is appointed to the

ASRI steering committee and has responsibility for local oversight. All sub-investigators are Consultant Rheumatologists. Accuracy of the data collected is monitored quarterly by a trained study nurse employed for this purpose.

2.2.1.4 Informed consent & ethics

Written informed consent is obtained locally from all patients by a trained investigator. Ethical approval for ASRI was originally obtained from the Tallaght University Hospital/St. James's Hospital Joint Research Ethics Committee (REC reference: 2013/21/06, see Appendix C). Each participating centre subsequently received ethical approval from their respective Research Ethics Committee. No specific additional ethics was required for this project, as it was within the remit of the aims and objectives of the original application.

2.2.1.5 Data collection

In each centre, a trained study sub-investigator (nurse or doctor) collected patient data according to the standard ASRI protocol in a structured face-to-face visit. The medical record was reviewed as required to obtain information not available directly from the patient. Data collected was then entered into an electronic centralised report form:

- Demographics: age, sex, ethnicity, marital status, employment status, alcohol intake, smoking status (current/past/never).

- Disease characteristics: age of symptom onset, duration of disease, delay to diagnosis, presence at any time of extra-articular manifestations (EAM) (uveitis, psoriasis, inflammatory bowel disease), presence at any time of other SpA features (enthesitis, dactylitis, peripheral arthritis), family history of SpA (AS, AxSpA, psoriasis or psoriatic arthritis), human leukocyte antigen (HLA)-B27 status, highest recorded erythrocyte sedimentation rate (ESR), current ESR (measured on the day), highest recorded C-reactive protein (CRP), current CRP (measured on the day), mNY criteria, ASAS criteria, presence or absence of sacroiliitis on x-ray and MRI imaging.

- Treatment history: current and previous treatment with non-steroidal anti-inflammatories (NSAIDs), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) including methotrexate and sulfasalazine, biologics (tumour necrosis factor inhibitors (TNFi).

- Morbidities: considered present if a condition was diagnosed by a physician; information collected through history-taking from patient, patient medical records additionally used as required to confirm the presence or absence of each of these

morbidities. Information was collected on the following conditions known to be prevalent in SpA (Molto et al., 2016): ischaemic heart disease (IHD), cerebrovascular disease, hypertension (HTN), hyperlipidaemia, diabetes mellitus, peptic ulcer disease (PUD), tuberculosis (TB), osteoporosis, depression, cancer (melanoma, non-melanoma skin cancer, lung, breast, gastrointestinal, genitourinary, lymphoma, haematological, other). Additionally obesity (recorded as a body mass index (BMI) of greater than 30 mg/kg^2, as per the WHO criteria, based on the weight and height measurements taken by the investigator during the assessment) and alcohol excess (considered as an alcohol consumption of greater than 21 units in men and 14 units in women, as per national guidelines (Health Service Executive, 2015), and was based on the patient's self-report of alcohol consumption) were collected. EAMs were not considered as additional morbidities.

- Physical examination: each sub-investigator was trained in the technique of the following standardised measurements: tragus-to-wall, cervical rotation, chest expansion, modified Schober test, lumbar side flexion, intermalleolar distance – all performed according to standardised technique (Jenkinson et al., 1994); additionally current blood pressure (measured in mmHg), height (measured in centimetres), weight (measured in kilograms) and waist circumference (measured in cm) were performed.

- DXA: most recent DXA result was obtained (if performed) and osteoporosis defined according to the WHO (1993).

2.2.2 Outcome measures

The validated outcome measures used in this study have been described in detail in Section 1.9.1. They were completed by the patient on the day of assessment and entered in the electronic record by the sub-investigator performing the assessment:

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- Bath AS Functional Index (BASFI)
- Health Assessment Questionnaire (HAQ)
- AS Quality of Life (ASQoL)
- Bath AS Metrology Index (BASMI).

2.2.3 Multimorbidity

In this study, a morbidity is defined as the presence of a chronic condition in a patient, as diagnosed by a physician. Multimorbidity is defined as the presence of at least two chronic conditions in one person, in line with the standard definition adopted in the existing literature (Almirall and Fortin, 2013, van den Akker et al., 1996). Severity of multimorbidity was assessed by counting the number of chronic conditions in addition to axSpA present in an individual (Hanlon et al., 2018, Radner et al., 2015c). Of note, EAMs were not considered a separate morbidity.

2.2.4 Statistical analysis

Descriptive statistics are presented as mean with standard deviation (SD) for normally distributed continuous variables, median with 25^{th} and 75^{th} percentiles for non-normally distributed continuous variables or frequencies with percentage for categorical variables. Independent two-tailed T-tests, Mann-Whitney U test or Analysis of Variance (ANOVA) were performed on continuous data as indicated to explore differences between groups. Chi-square tests compared categorical variables. Tukey's honestly significant difference (HSD) test controlled for multiple comparisons.

We developed separate models to determine the association between (1) being multimorbid and (2) worsening multimorbidity (defined by the count of chronic conditions) and disease outcome measures. Individual models were developed with BASDAI, BASMI, BASFI, ASQoL and HAQ as the dependent variable. Initially we explored univariable demographic, treatment and disease-related characteristics associated with each outcome. To control for the effects of these characteristics, we built a model using all variables with a p-value of <0.1 in univariable analysis and performed hierarchical regression, entering variables in blocks of demographics, treatment and disease-related variables prior to assessing the effect of multimorbidity. Adjusted R^2 was used as a measure of fit to determine the additional variation in the dependent variable explained by each block of variables entered. Age and gender were controlled for in every model, as these were considered clinically significant variables. The appropriate assumptions for each statistical test were met. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 24.

2.3 Results

2.3.1 Baseline characteristics of ASRI cohort

2.3.1.1 Demographics

At time of database extraction, the ASRI cohort contained 734 patients, from twelve Rheumatology centres representing all geographical regions of Ireland. Seventy-seven percent (n=536) of the patients in ASRI were male, with a mean (SD) age of 45 (12) years and a median (IQR) disease duration of 16 (9 to 27) years. The baseline demographic and clinical characteristics of the ASRI cohort are outlined in Table 2-1.

2.3.1.2 Treatment patterns in ASRI cohort

Over half of the cohort (54.8%, n=402) was currently taking NSAIDs, with 66.4% (n=267) taking NSAIDs on an intermittent basis. The majority (80.5%, n=591) had never taken csDMARDs, with only 9.9% (n=73) of patients in the cohort currently taking csDMARDs, and 9.5% (n=70) having previously taken them. With regards to biologics, 62.1% (n=456) of patients were currently using TNF-inhibitor, 7.6% (n=56) were previously taking a TNF-inhibitor but had discontinued treatment and 30.2% (n=222) had never taken a TNF-inhibitor. Etanercept was the most frequently used biologic, taken by 38% (n=279) of patients, followed by adalimumab (35.3%, n=259), golimumab (13.2%, n=97), infliximab (9.7%, n=71) and certolizumab (2.6%, n=19). In patients who had ever taken biologic medication, the median (25^{th}, 75^{th} percentile) number of biologics used was 1 (1, 2); 47.5% (n=349) of the cohort had used one biologic, 16.3% (n=120) had used two, 5% (n=37) had used three, 0.7% (n=5) had used four and one patient had used five biologics. Figure 2-1 outlines the current treatment combination, with TNF-inhibitor treatment alone the most common choice (33%, n=242), followed by the combined use of TNF-inhibitor and NSAID (23.2%, n=170).

2.3.2 Co-morbidity profile of ASRI cohort

2.3.2.1 Prevalence of comorbidities

In this cohort, 25% (n=180) of patients had one comorbidity, 16% (n=118) had two comorbidities, 8% (n=57) had three comorbidities and 7% (n=48) had four or more comorbidities. The most prevalent comorbidity was obesity, affecting 27% (n=192) of the population, followed by hypertension (n=155, 21%), hyperlipidaemia (n=119, 16%) and depression (n=76, 10%). Thirty percent (n=222) of patients had cardiovascular comorbidity i.e. at least one of IHD, cerebrovascular disease, hypertension, hypercholesterolaemia. The prevalence of all comorbidities is outlined in Figure 2-2.

Table 2-1: Baseline characteristics of Ankylosing Spondylitis Registry of Ireland (ASRI) cohort, with comparison between individuals with and without multimorbidity.

	Whole population *(n=734)*	AxSpA only *(n=331)*	Multimorbid *(n=403)*	P value†
Males	563 (76.7)	251 (75.8)	312 (77.4)	0.61
Age, *years*	45 (12.4)	39.6 (10.7)	49.5 (12)	**<0.01**
Disease duration, *years*	16 (9, 27)	13 (7, 20)	20 (12, 32)	**<0.01**
Delay to diagnosis, *years*	6 (2, 11)	5 (2,10)	7 (3, 13)	**<0.01**
Caucasian	708 (96.5)	311 (94)	397 (98.5)	**<0.01**
mNY criteria	570 (77.7)	247 (74.6)	323 (80.1)	0.07
ASAS criteria	690 (94)	313 (94.6)	377 (93.5)	0.57
HLA-B27 positive*	502 (91.1)	238 (91.9)	264 (90.4)	0.54
Unemployed[¶]	166 (22.6)	60 (18.1)	106 (26.3)	**0.01**
Smoker				
Current smoker	219 (29.8)	106 (32)	113 (28)	**0.02**
Ex-smoker	207 (28.2)	76 (23)	131 (32.5)	**0.02**
BMD[ł]**,** *T-score*				
Hip	-1.2 (1.1)	-1.3 (0.8)	-1.1 (-2, -0.1)	0.38
Spine	-0.7 (1.9)	-0.9 (1.2)	-0.7 (-2.3, 1.2)	0.30
Waist circumference, *cm*	95 (85, 104)	88 (81, 96)	101 (91, 110)	**<0.01**
ESR[§]**,** *mm/h*	10 (5, 20)	10 (5, 19)	11 (5, 22)	0.09
CRP[§]**,** *mg/L*	3 (1, 7.7)	2.5 (1, 7)	3 (1, 8)	0.18
BMI, kg/m^2	26.6 (23.9, 30.3)	24.7 (22.9, 27)	29.5 (26, 32.9)	**<0.01**
Extra-spinal manifestations				
Peripheral arthritis	239 (33.3)	89 (27.4)	150 (38.2)	**<0.01**
Enthesitis	125 (17.5)	49 (15.2)	76 (19.3)	0.14
Uveitis	256 (35.7)	109 (33.6)	147 (37.4)	0.30
Dactylitis	50 (7)	17 (5.2)	33 (8.4)	0.10
Psoriasis	131 (18.2)	47 (14.5)	84 (21.3)	**0.02**
IBD	71 (9.9)	26 (8)	45 (11.2)	0.13
Treatment history				
Current NSAIDs	373 (50.8)	155 (46.8)	218 (54.1)	0.05
Current sulfasalazine	29 (4)	13 (3.9)	16 (4)	0.14
Current methotrexate	47 (6.4)	11 (3.3)	36 (8.9)	0.25
Lifetime TNFi use	512 (69.8)	229 (69.2)	283 (70.2)	0.76
Current TNFi	456 (62.1)	207 (62.5)	249 (61.8)	0.84

*Data are mean (SD), median (25^{th} quartile, 75^{th} quartile) or n (%). * HLA-B27 status unknown in n=183 patients.* [¶]*Patients within employment age but unemployed. † Comparison between axSpA-only and multimorbid patient groups (Independent T-tests for continuous variables, Chi-square analysis for categorical variables), significant differences highlighted in bold.* [ł]*Most recent BMD results.* [§]*Refers to values at time of recruitment. ASAS: Assessment of SpondyloArthritis Society; ASQoL: Ankylosing Spondylitis Quality of Life Index; AxSpA: axial spondyloarthropathy; BASDAI: Bath AS Disease Activity Index; BASFI: Bath AS Functional Index; BASMI: Bath AS Metrology Index; BMD: bone mineral density; HAQ: Health Assessment Questionnaire; HLA: Human leucocyte antigen; IBD, inflammatory bowel disease; IBD: Inflammatory Bowel Disease; mNY: modified New York; NSAIDs: Non-steroidal anti-inflammatory drugs; TNFi: Tumour necrosis factor inhibitor.*

Figure 2-1: Current pharmacological treatment of individuals in the ASRI cohort. Data presented is prevalence (%). DMARD: disease-modifying antirheumatic drugs; NSAID: non-steroidal anti-inflammatory drugs; TNF: tumour necrosis factor inhibitor.

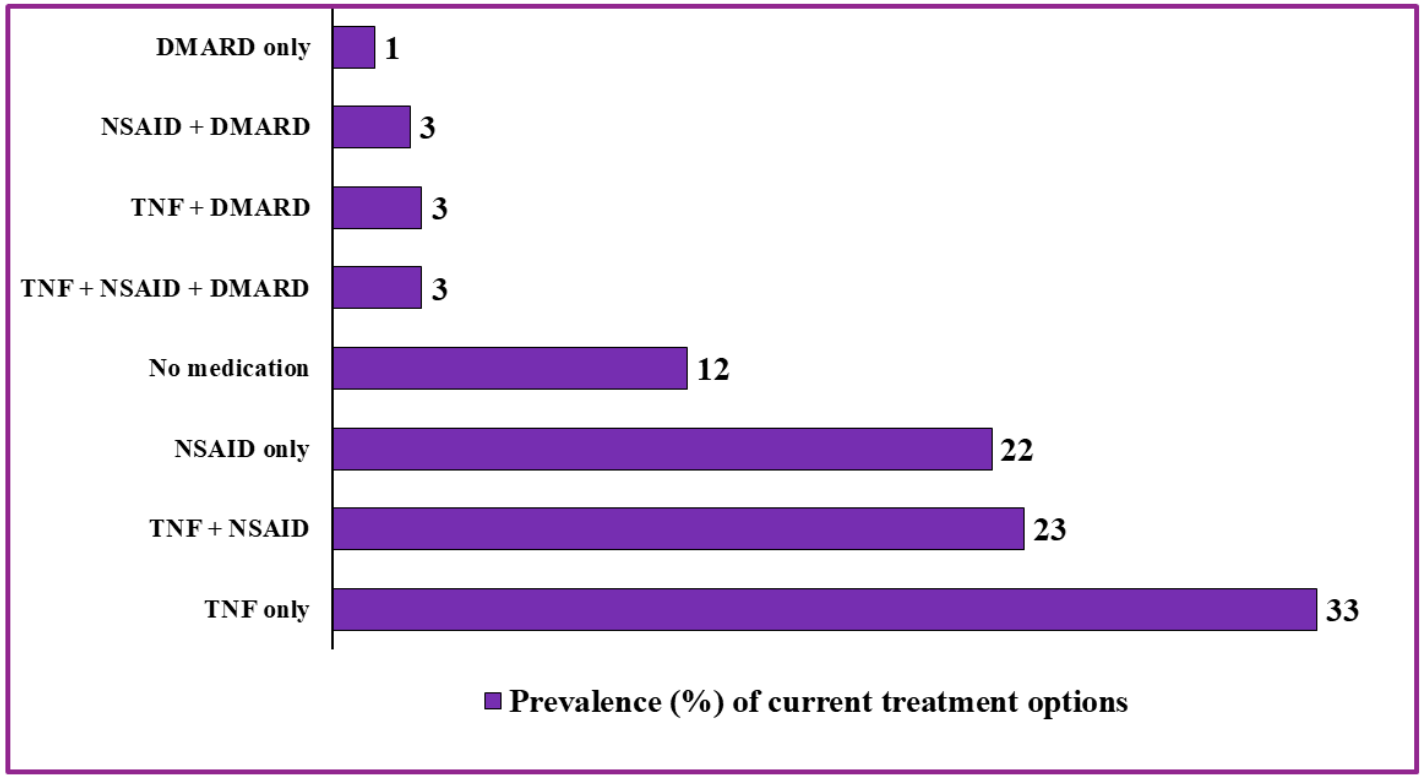
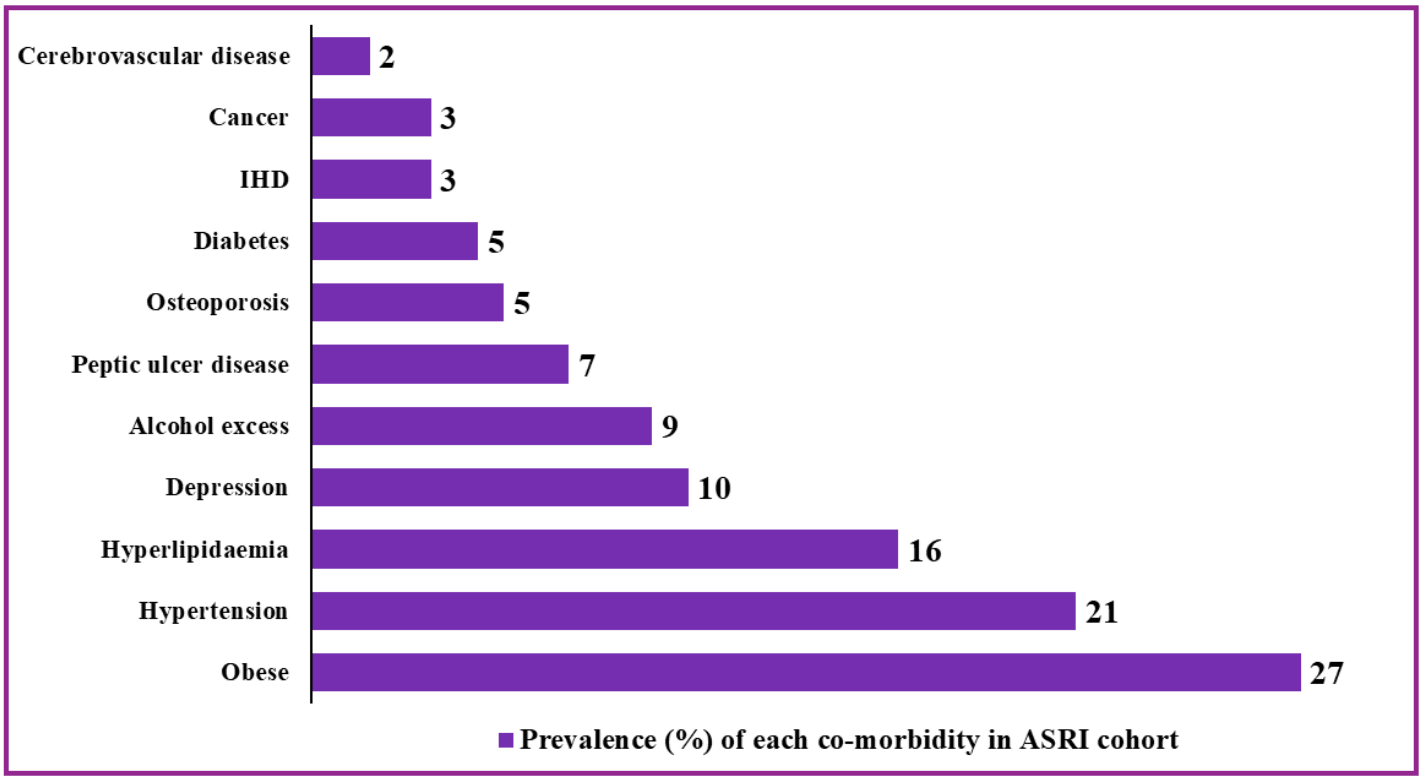


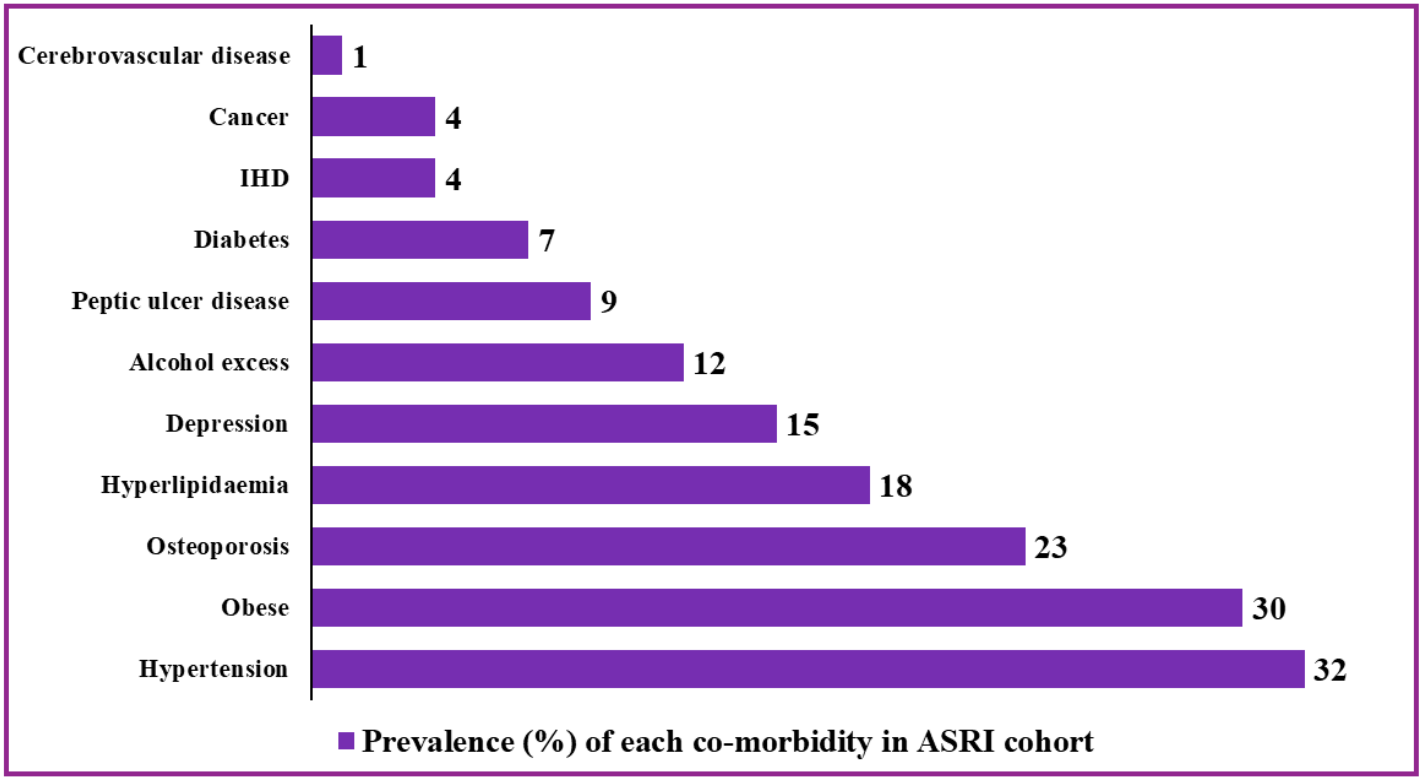
Figure 2-2: Prevalence of comorbidities in Ankylosing Spondylitis Registry of Ireland (ASRI) cohort, ranked from least to most common. IHD, ischaemic heart disease.



2.3.2.2 Osteoporosis

Thirty-nine patients (5.3%) reported receiving a prior diagnosis of osteoporosis from a physician or had a diagnosis of osteoporosis recorded in their medical record. Only 19.5% (n=143) of patients had previously had a DXA. The most recent available DXA results were collated – 100 DXA results were obtained, consisting of 95 hip and 94 spine results; the remaining DXA scans were performed in facilities where investigators were unable to access results. The mean age of this subgroup was 51.9 (SD 11.6) years, with 82% (n=82) male. Fifty-six participants were aged 50 years or over: 84% (n=47) were male and the mean age was 60.2 (SD 7.4) years. Postmenopausal status for women was unavailable. Of all the available DXA results, 58% of patients had low BMD at the hip (43% osteopenia, 15% osteoporosis) and 50% had low BMD at the spine (33% osteopenia, 17% osteoporosis). In total, 23% (n=23) of patients had osteoporosis on DXA of at least one site (i.e. osteoporosis of the hip and/or spine). Of the participants aged 50 years or over, 53% had low BMD at the hip (32% osteopenia, 21% osteoporosis) and 39% had low BMD at the spine (22% osteopenia, 18% osteoporosis). In the subgroup of patients with available DXA data, osteoporosis was the third most common comorbidity, after hypertension and obesity (see Figure 2-3).

Figure 2-3: Prevalence of comorbidities in the subgroup of patients (n=100) in the Ankylosing Spondylitis Registry of Ireland (ASRI) cohort with available DXA data, ranked from least to most common. IHD, ischaemic heart disease.



2.3.3 Multimorbidity in axSpA

2.3.3.1 Comparison of baseline characteristics between multimorbid and non-multimorbid patients

Fifty-five percent (n=403) of the cohort was multimorbid i.e. had at least one comorbidity in addition to axSpA. Multimorbid patients were older, with longer disease duration and longer delay to diagnosis than axSpA-only patients (see Table 2-1). Gender and HLA-B27 status had no effect on the presence or absence of multimorbidity. Multimorbid patients had similar CRP and ESR to the axSpA-only cohort. The prevalence of psoriasis was higher in multimorbid patients than axSpA-only patients (21% versus 15%, p=0.02). Uveitis and IBD were equally prevalent in both groups. The use of TNF-inhibitors was similar in both groups. More multimorbid patients used NSAIDs than patients with axSpA only (54% versus 47%), but this did not reach statistical significance (p=0.05).

2.3.3.2 Association between multimorbidity and disease outcomes

Across all disease outcome measures, patients with multimorbidity had significantly higher mean scores than those patients with axSpA-only (see Table 2-2). The cohort was further analysed according to the burden of comorbidity: (a) patients with axSpA-only, (b) multimorbid patients with one comorbid condition, and (c) multimorbid patients with two or more comorbidities. ANOVA revealed significant between-group differences for all outcomes (see Table 2-3). Although all disease outcome measures were higher in patients with one compared to no comorbidity, only BASMI, BASFI and HAQ were significantly higher in patients with two or more comorbidities when compared to patients with one comorbidity. There was no difference in BASDAI and ASQoL scores between the multimorbid cohort with two or more comorbidities and one comorbidity (see Table 2-2).

Table 2-2: Comparison of disease outcome measures between multimorbid patients and patients with axial spondyloarthropathy. Also included is subgroup analysis of increasing comorbidity burden.

						Tukey's HSD Comparisons†	
Disease outcome	**AxSpA only (Mean (SD))**	**Multimorbid (Mean (SD))**	**Mean difference (95% CI)**	**Subgroups**	**Mean (SD)**	***axSpA only (95% CI)***	***1 comorbidity (95% CI)***
BASDAI	3.46 (2.39)	4.47 (2.36)	1.00 (0.66 to 1.35)*	1 comorbidity	4.23 (2.40)	0.24 to 1.28*	…
				≥ 2 comorbidities	4.66 (2.31)	0.72 to 1.68*	-0.12 to 1.00
BASFI	2.66 (2.36)	4.44 (2.62)	1.78 (1.42 to 2.14)*	1 comorbidity	4.01 (2.56)	0.81 to 1.89*	…
				≥ 2 comorbidities	4.78 (2.62)	1.62 to 2.63*	0.19 to 1.36*
BASMI	2.72 (2.26)	4.29 (2.58)	1.57 (1.21 to 1.93)*	1 comorbidity	3.65 (2.54)	0.39 to 1.46*	…
				≥ 2 comorbidities	4.80 (2.50)	1.59 to 2.58*	0.58 to 1.73*
ASQoL	5.18 (5.32)	7.71 (5.59)	2.53 (1.73 to 3.33)*	1 comorbidity	7.50 (5.51)	1.12 to 3.51*	…
				≥ 2 comorbidities	7.88 (5.67)	1.59 to 3.82*	-0.90 to 1.68
HAQ	0.39 (0.45)	0.65 (0.56)	0.26 (0.19 to 0.33)*	1 comorbidity	0.57 (0.51)	0.07 to 0.29*	…
				≥ 2 comorbidities	0.72 (0.59)	0.22 to 0.43*	0.03 to 0.27*

**Denotes significant difference.*

ASQoL: Ankylosing Spondylitis Quality of Life index; axSpA: axial spondyloarthropathy; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CI: confidence interval; HAQ: Health Assessment Questionnaire; HSD: Honestly Significant Difference; N: number of patients; SD: standard deviation.

Table 2-3: Analysis of Variance (ANOVA) investigating differences in disease outcome measures of the Ankylosing Spondylitis Registry of Ireland (ASRI) cohort between three groups: (1) axSpA only, (2) multimorbid with one additional chronic condition, and (3) multimorbid with two or more additional chronic conditions.

Source of variation	Df	Sums of squares	Mean Square	F	P
BASDAI:					
Group	2	199.8	99.9	17.8	<0.001
Error	722	4046.0	5.6	—	—
BASFI:					
Group	2	636.4	318.2	51.3	<0.001
Error	731	4534.1	6.2	—	—
BASMI:					
Group	2	564.6	282.3	48.7	<0.001
Error	710	4112.9	5.8	—	—
ASQoL:					
Group	2	1174.5	587.2	19.6	<0.001
Error	729	21850.8	30.0	—	—
HAQ:					
Group	2	14.5	7.2	28.0	<0.001
Error	728	188.5	0.3	—	—

ASQoL: Ankylosing Spondylitis quality of life; BASDAI: Bath Ankylosing Spondylitis disease activity index; BASFI: Bath Ankylosing Spondylitis functional index; BASMI: Bath Ankylosing Spondylitis Metrology Index; Df: degrees of freedom; F: F ratio; HAQ: health assessment questionnaire.

2.3.4 Regression analysis

In adjusted analyses (see Table 2-4), when compared to patients with axSpA only, being multimorbid was independently associated with a higher BASDAI of 0.7 (95% CI 0.34 to 1.05), BASMI of 0.45 (95% CI 0.09 to 0.80), BASFI of 0.5 (95% CI 0.23 to 0.78), HAQ of 0.07 (95% CI 0.00 to 0.13) and ASQoL of 0.87 (95% CI 0.28 to 1.46).

In separate models investigating the association between the number of comorbidities and disease outcome measures (see Table 2-5), the presence of each additional co-morbidity was independently associated with a higher BASDAI of 0.23 (95% CI 0.09 to 0.37), BASMI of 0.20 (95% CI 0.05 to 0.34), ASQoL of 0.25 (95% CI 0.02 to 0.49), HAQ of 0.03 (95% CI 0.01 to 0.06) and BASFI of 0.21 (95% CI 0.10 to 0.32).

Table 2-4: Adjusted analyses of association between disease outcome measures (dependent variables in individual models) and presence of multimorbidity.

Independent variables	Dependent variables				
	BASDAI	*BASFI*	*BASMI*	*ASQoL*	*HAQ*
	ß (95% CI)	*ß (95% CI)*	*ß (95% CI)*	*ß (95% CI)*	*ß (95% CI)*
Age	0.01 (-0.01 to 0.02)	0.05 (0.04 to 0.06)	0.09 (0.08 to 0.11)	-0.01 (-0.03 to 0.02)	0.01 (0.00 to 0.01)
Gender (male v female)	-0.94 (-1.32 to -0.56)	-0.19 (-0.49 to 0.11)	0.50 (0.11 to 0.89)	-0.55 (-1.10 to 0.09)	-0.07 (-0.15 to -0.01)
Multimorbid (yes v no)	0.70 (0.34 to 1.05)	0.50 (0.23 to 0.78)	0.45 (0.09 to 0.80)	0.87 (0.28 to 1.46)	0.07 (0.00 to 0.13)
BASDAI	§	0.68 (0.62 to 0.73)	§	1.64 (1.52 to 1.76)	0.12 (0.10 to 0.13)
Unemployed (yes v no)	1.62 (1.23 to 2.00)	0.84 (0.52 to 1.15)	1.48 (1.09 to 1.87)	1.39 (0.72 to 2.05)	0.21 (0.13 to 0.28)
Current/past smoker (yes v no)	0.39 (0.07 to 0.71)	0.31 (0.06 to 0.57)	‡	‡	‡
NSAIDs use (yes v no)	1.04 (0.72 to 1.36)	‡	†	‡	‡
ESR	‡	‡	0.03 (0.02 to 0.04)	‡	‡

Variables tested in univariable regression: age, gender, unemployed, delay to diagnosis, current or past smoker, enthesitis, arthritis, dactylitis, uveitis, IBD, psoriasis, CRP, ESR, multimorbid, HLA-B27 positivity, NSAIDs use, conventional synthetic DMARDs use, current TNFi use, lifetime history of TNFi use.

Variables not included in the above table were judged not to improve the fit of any of the final models. Every model controlled for age and gender.

† P > 0.1 in univariable analysis. ‡ P > 0.05 in multivariable analysis. §: not assessed.

ASQoL: Ankylosing Spondylitis Quality of Life score; ß: regression coefficient; BASDAI: Bath Ankylosing Spondylitis disease activity index; BASFI: Bath Ankylosing Spondylitis functional index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CI: confidence interval; CRP: C-reactive protein; DMARDs: disease-modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire; HLA: human leucocyte antigen; IBD: inflammatory bowel disease; MRI: magnetic resonance imaging; NSAIDs: non-steroidal anti-inflammatories; TNFi: tumour necrosis factor-inhibitor.

Table 2-5: Adjusted analyses of association between disease outcome measures (dependent variables) and severity of multimorbidity

Independent variables	Dependent variables				
	BASDAI ß *(95% CI)*	*BASFI* ß *(95% CI)*	*BASMI* ß *(95% CI)*	*ASQoL* ß *(95% CI)*	*HAQ* ß *(95% CI)*
Age	0.01 (-0.01 to 0.02)	0.05 (0.04 to 0.06)	0.09 (0.07 to 0.11)	-0.01 (-0.03 to 0.02)	0.01 (0.00 to 0.01)
Gender (male v female)	-0.89 (-1.26 to -0.49)	-0.07 (-0.37 to 0.23)	0.64 (0.23 to 1.04)	-0.35 (-0.99 to 0.30)	-0.04 (-0.11 to 0.04)
Worsening multimorbidity	0.23 (0.09 to 0.37)	0.21 (0.10 to 0.32)	0.20 (0.05 to 0.34)	0.25 (0.02 to 0.49)	0.03 (0.01 to 0.06)
BASDAI	§	0.73 (0.67 to 0.78)	§	1.72 (1.61 to 1.84)	0.12 (0.11 to 0.14)
Delay to diagnosis	‡	‡			-0.01 (-0.01 to -0.00)
Unemployed (yes v no)	1.68 (1.29 to 2.07)	†	†	†	†
Current/past smoker (yes v no)	0.38 (0.05 to 0.71)	0.58 (0.20 to 0.96)	‡	‡	‡
NSAIDs use (yes v no)	1.11 (0.79 to 1.44)	‡	‡	‡	‡
ESR	‡	‡	0.03 (0.02 to 0.04)	‡	0.00 (0.00 to 0.01)
IBD (yes v no)	0.74 (0.19 to 1.29)	‡	‡	‡	‡

† P > 0.1 in univariable analysis. ‡ P > 0.05 in multivariable analysis. §: not assessed.

Variables tested in univariable regression: age, gender, unemployed, delay to diagnosis, current or past smoker, enthesitis, arthritis, dactylitis, uveitis, IBD, psoriasis, CRP, ESR, multimorbid, HLA-B27 positivity, NSAIDs use, conventional synthetic DMARD use, current TNFi use, lifetime history of TNFi use.

Variables not included in the above table were judged not to improve the fit of any of the final models. Every model controlled for age and gender.

ASQoL: Ankylosing Spondylitis Quality of Life score; ß: regression coefficient; BASDAI: Bath Ankylosing Spondylitis disease activity index; BASFI: Bath Ankylosing Spondylitis functional index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CI: confidence interval; CRP: C-reactive protein; DMARDs: disease-modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire; HLA: human leucocyte antigen; IBD: inflammatory bowel disease; MRI: magnetic resonance imaging; NSAIDs: non-steroidal anti-inflammatories; TNFi: tumour necrosis factor-inhibitor.

2.4 Discussion

2.4.1 Summary of findings

In recent years, there is an increasing body of research exploring comorbidities in patients with axSpA, in recognition of the excess burden comorbidities add to disease. The overarching aim of this study was to examine the burden of comorbidity in individuals with axSpA in Ireland, the first large epidemiological study to do so.

The first objective of the study was to describe the profile of comorbidities in axSpA patients. Obesity was the single most common comorbidity in the study, affecting 27% of the cohort, followed by hypertension (21%) and hypercholesterolaemia (16%). The second objective was to assess the prevalence of multimorbidity in axSpA, which we determined was 55% in our ASRI cohort. The third objective was to assess relationships between multimorbidity in axSpA and disease outcome measures. Multimorbid patients in this study had worse disease outcome scores than patients without multimorbidity. In addition, the more comorbid conditions a patient had, the worse the disease outcome measures are. The final objective of the study was to assess the prevalence of osteoporosis in adults with axSpA in Ireland. We demonstrated that although the prevalence of osteoporosis in the whole cohort was low (5%), a minority (less than 20%) of patients had ever had an objective assessment of BMD. Within the subgroup of patients with an available DXA measurement, the prevalence of osteoporosis was much higher (23%).

2.4.2 Comparison of our findings with existing literature

Profile of comorbidities

The prevalence of hypertension and hypercholesterolaemia was lower in our study than in the international ASAS-COMOSPA study, but the frequency of ischaemic heart disease (3%) and cerebrovascular disease (2%) was similarly low (Molto et al., 2016). Cardiovascular comorbidity was common (30%) in our study, reflecting international trends (WHO, 2015). Depression was prevalent in our study, affecting 10% of patients, as was alcohol excess (9%).

Few studies exist which have reported data on obesity in axSpA, as many prior studies which have investigated comorbidities did not report prevalence figures for obesity (Walsh et al., 2018, Molto et al., 2016). One exception is data reported from the SPondyloArthritis Caught Early (SPACE) cohort (Rubio Vargas et al., 2016), which reported a prevalence of 11.9% for obesity in 168 individuals with axSpA, much lower than that reported in this study. The prevalence of obesity in our study mirrors the prevalence of the general population in Ireland, where 25% of adults ≥ 20 years of age are obese, according to the WHO (World Health Organization, 2013),

one of the highest prevalence rates in Europe. Patients in the SPACE cohort were recruited from centres in Norway, Netherlands and Italy, countries where background obesity rates range from 19% in the Netherlands, to 20% in Italy and 22% in Norway (World Health Organization, 2013).

Prevalence of multimorbidity

This is the first study in axSpA to move beyond focusing exclusively on comorbidity and to consider the broader concept of multimorbidity. There is growing interest in multimorbidity in the general population. Multimorbid patients have complex needs, requiring cohesive individualised patient-centred strategies, rather than the traditional disease-focused model of care, in order to meet the needs of a rapidly expanding population (Navickas et al., 2016). The negative consequences of multimorbidity are well-outlined in the general population (Menotti et al., 2001, Cassell et al., 2018, Barnett et al., 2012), but much less is known about its impact in axSpA patients. Our study found multimorbidity is common in axSpA patients, affecting over half (55%) of this large well-characterised cohort. Additionally, multimorbidity is associated with worse disease outcomes than those with axSpA alone.

Comparing our findings on multimorbidity with the existing literature is challenging. In the first instance, there is no gold standard definition of multimorbidity (Diederichs et al., 2011). Additionally, research into multimorbidity in rheumatic diseases is limited (Radner et al., 2015c, van der Zee-Neuen et al., 2016), with no studies to our knowledge looking at multimorbidity in axSpA. The prevalence of multimorbidity in our cohort is higher than that reported in the general population, where the prevalence of multimorbidity is around 23% (Barnett et al., 2012). However, estimates vary in the general population from 13% to 95% (Violan et al., 2014, Hanlon et al., 2018) depending on the age-group and definition of multimorbidity used. The prevalence of multimorbidity is unsurprisingly higher in primary care populations than the general population (Mokraoui et al., 2016). It has been shown that musculoskeletal diseases (MSD) are common in patients with multimorbidity (Simoes et al., 2017) and amplify the impact on physical health (van der Zee-Neuen et al., 2016). Multimorbidity has also been demonstrated as prevalent in RA, affecting over 60% of patients (Radner et al., 2015c), therefore it is unsurprising that multimorbidity is also common in axSpA patients.

In our study, we defined the differences between multimorbid and axSpA-only patients. Multimorbid axSpA patients had longer disease duration, longer delay to diagnosis and were on average ten years older than patients with axSpA only, a similar trend to other populations where multimorbidity increases with age (Barnett et al., 2012, Agborsangaya et al., 2013). However, in our study, the average age of multimorbid axSpA patients was 50 years, which is younger than that seen in primary care practice populations and in RA (Radner et al., 2015b, Barnett et al.,

2012). Therefore, our study demonstrates that not only is multimorbidity common in axSpA, but it is not exclusive to the elderly in axSpA.

Males and females were equally affected by multimorbidity in our study. A systematic review of the general population found an association between women and multimorbidity (Violan et al., 2014). However, literature is conflicting in RA, where both no gender effect (Radner et al., 2015b) and a predominance of women in the multimorbid group (Armagan et al., 2018) have been shown.

Obesity is not always included in multimorbidity scores, with it only counted as a chronic condition in five of 39 multimorbidity counts in a systematic review in 2011 (Diederichs et al., 2011). However, obesity was only officially recognised as a disease in 2013 (Kyle et al., 2016). As obesity has a clear negative impact on mortality (Flegal et al., 2013) and represents a growing public health challenge, it is worthy of being considered in a multimorbidity count (Agborsangaya et al., 2013), thus our decision to include it.

Implications of multimorbidity in axSpA

In this study, we also demonstrate an association between multimorbid patients and worse disease outcomes, as assessed by both subjective and objective outcome measures. We also demonstrate that as the severity of multimorbidity increases, measured by a count of each comorbidity present, so too do disease outcome scores. Our results reflect research carried out in the general population, where multimorbidity is associated with impaired function and worse quality of life, particularly if a rheumatic disease is involved (Loza et al., 2009), and RA, where multimorbid patients have more severe disease and more fatigue than patients with RA only (Radner et al., 2015b, Tournadre et al., 2018). Nikiphorou et al (Nikiphorou et al., 2018) similarly demonstrated that a rising comorbidity burden is associated with worse QoL in SpA patients.

However, what differentiates our study from those which focus on co-morbidity alone, is that we demonstrate that simply being multimorbid, i.e. having any additional condition to axSpA, is associated with worse outcomes compared to patients with axSpA alone. The difference in outcomes between axSpA-only and being multimorbid is more marked than the difference for each additional condition thereafter. This has potential to be a clinically useful finding, which could provide physicians with a simple method to identify patients at risk of poor outcomes.

Osteoporosis prevalence

In ASAS-COMOSPA, osteoporosis was the most frequent co-morbidity, affecting 13% of the cohort (Molto et al., 2016). When we examined the prevalence of osteoporosis in our entire cohort, recorded as a diagnosis either documented in the medical record or reported as physician-

diagnosed by the patient, the prevalence was 5.3%. However, less than 20% of the cohort had ever had a DXA assessment of their BMD. Thus, when we examined only the subgroup of the cohort with available DXA results, the prevalence of osteoporosis occurring in at least one site (hip and/or spine) was much higher, at 23%, now becoming the third most common comorbidity. This figure is even more startling when the demographics of the subgroup with DXA results is considered: average age of 52 years and predominantly (82%) male. The prevalence of osteoporosis in all men over the age of 50 years is estimated at just under 7% (Hernlund et al., 2013), thus the prevalence in our study is unexpectedly high.

It must be noted that this osteoporosis prevalence of 23% on DXA is likely to be an over-estimation of the true prevalence of osteoporosis in axSpA in Ireland: individuals with axSpA referred for DXA assessment may have had risk factors for low BMD which prompted the referral, making a diagnosis of osteoporosis in that subgroup more probable, representing a bias. Therefore, the true prevalence is expected to fall between 5% and 23%, closer to the prevalence of 13% reported in ASAS-COMOSPA (Molto et al., 2016). This is the first study to demonstrate a high prevalence of osteoporosis amongst individuals with axSpA in Ireland.

2.4.3 Limitations

Firstly, the cross-sectional design of this registry study prohibits comment on causality, therefore we can merely observe the association between multimorbidity and severe disease. Secondly, the absence of information on co-morbidities not collected within the framework of ASRI represents a potential limitation. However, our study reports the co-morbidities known to occur most commonly in SpA, as outlined in ASAS-COMOSPA (Molto et al., 2016), with the exception of infections. In ASAS-COMOSPA, the hepatitis B prevalence was 3.5% in SpA worldwide. In Ireland the prevalence of hepatitis B is known to be very low (<0.1%) (Schweitzer et al., 2015), therefore not collecting data on the prevalence of hepatitis B is unlikely to have influenced the results. Additionally, pulmonary disease is not collected in ASRI. However, although abnormalities on high-resolution computed-tomography imaging of the thorax are common (El Maghraoui and Dehhaoui, 2012), the clinical significance of these is unknown (Ozdemir et al., 2012), therefore we are confident that not including a measure of the prevalence of pulmonary disease is unlikely to have significantly affected the prevalence of multimorbidity. Thirdly, alcohol intake is based on patients own report. It has been well established that patients tend to underestimate their alcohol consumption. All efforts were made to establish an accurate alcohol intake, but it is possible that intake was under-reported, thus under-estimating the prevalence of alcohol excess. Fourthly, our population is overwhelmingly Caucasian, therefore extrapolating

the results of our study to other ethnicities is not possible. Finally, T-scores alone were used to calculate prevalence of osteoporosis, due to the lack of availability of Z-scores, which are preferred in men under 50 years and pre-menopausal women (Shepherd et al., 2015).

2.4.4 Strengths

This is a large study, with a well characterised cohort. The homogenous nature of our patients, who are overwhelmingly Caucasian and HLA-B27 positive, reduces variation that could be introduced from diverse backgrounds. Our study contains real-life data, providing clinicians with relevant and clinically useful information. It is also novel, as to our knowledge it is the first study to examine prevalence estimates of multimorbidity in axSpA. To date, studies have primarily focused on individual comorbidities in axSpA, along with their impact on disease outcomes/management. The danger with continuing to focus solely on individual comorbidities is the risk of taking the focus away from the patient; in the model of comorbidity, different conditions are considered the index disease by different clinicians, all aiming for best control of their disease of interest, without necessarily considering its impact on other diseases, potentially leading to fragmented care (Navickas et al., 2016, Radner et al., 2014). Multimorbidity brings the focus to the patient, not the disease, allowing patient-centred care to be delivered. However, comorbidity and multimorbidity are not mutually exclusive, therefore a wide breadth of knowledge of both is required for the optimal management of axSpA patients.

2.4.5 Future directions

Considering the association between multimorbidity and poor disease outcome measures, prospective longitudinal studies are needed to investigate the development of multimorbidity in axSpA and delineate its impact on disease outcomes over time. However, in order to be in a position to influence the prevalence of comorbidities in axSpA, it is critical to fully understand the comorbidities which occur at an increased prevalence in axSpA patients. In particular, the prevalence of osteoporosis in patients with an objective assessment of their BMD was unexpectedly high (23%) for a group of predominantly (82%) men with an average age of 52 years. Also, the low prevalence of DXA assessment indicates that assessment of bone health is not considered important or a priority in individuals with axSpA. Therefore, the epidemiology and impact of osteoporosis in axSpA represents an unmet need, and further research is required.

2.5 Conclusions

In summary, multimorbidity is prevalent in adults with axSpA, affecting over half of the cohort, and the presence of multimorbidity in axSpA is associated with worse disease outcomes. In addition, osteoporosis occurs at an unexpectedly high prevalence (23%) in individuals with axSpA, highlighting the need for further research.

Chapter 3 The paradox of osteoporosis in axial spondyloarthropathy

Material from this chapter has been disseminated in the following publication:

Fitzgerald G, O' Shea F. (2017) The fascinating paradox of osteoporosis in axial spondyloarthropathy. *Journal of Rheumatology*. 44(12):1767-76.

(full manuscript in Appendix A2).

3.1 Introduction

The cross-sectional epidemiological study presented in Chapter 2 outlined the prevalence of comorbidities in individuals with axSpA, particularly emphasising the high prevalence of osteoporosis. However, it must be acknowledged that the prevalence reported in a national epidemiological registry study may over-estimate the true prevalence of osteoporosis, due to the potential for selection bias, whereby individuals with increased risk factors for osteoporosis may have been more likely to be referred for DXA assessment, and thus receive a diagnosis of osteoporosis. However, taken in combination with the ASAS-COMOSPA study, where osteoporosis affected 13% of the cohort, it is clear that osteoporosis is a significant issue in individuals with axSpA.

Chapter 1 introduced osteoporosis in the general population, outlining its epidemiology and impact, as well as discussing the pathophysiology of osteoporosis. This chapter will aim to narratively review the topic of osteoporosis in inflammatory and rheumatic disease, in particular outlining the pathological bone remodelling that occurs in axSpA and summarising the existing literature regarding osteoporosis in axSpA. This will allow gaps in the literature to be identified, thus forming pertinent research questions.

3.2 Osteoporosis in chronic inflammatory disease

Osteoporosis, along with an increased susceptibility to fracture, is a recognised feature of chronic inflammatory disease. In RA, it is widely accepted that BMD is an extra-articular feature of the

disease, with the prevalence of osteoporosis up to twice that of the general population and an increased risk of fractures (Hauser et al., 2014, Lee et al., 2012, Lee et al., 2016, Jin et al., 2018, Xue et al., 2017, Kim et al., 2016, Chen et al., 2016). In juvenile idiopathic arthritis (JIA), generalised loss of BMD and an excess of fractures, both vertebral and non-vertebral, are noted (Huber and Ward, 2016). Individuals with systemic sclerosis (SSc) (Omair et al., 2013) and systemic lupus erythematosus (Wang et al., 2016) are also at risk of low BMD and fractures. In psoriatic arthritis (PsA), the data is less robust, but suggests a high prevalence of low BMD (Chandran et al., 2016, Kathuria et al., 2017). Osteoporosis is also recognised in non-rheumatic inflammatory conditions, such as chronic obstructive pulmonary disease (COPD) (Sarkar et al., 2015).

3.3 Bone remodelling in inflammatory disease

Osteoporosis in inflammatory disease is thought to be a result of an alteration in systemic bone remodelling, whereby bone resorption is increased and bone formation is reduced (Briot et al., 2017). Inflammation is characterised by the activation of both the innate and adaptive immune systems, which produce an array of inflammatory cytokines, which perpetuate inflammation, and activate bone resorption, as well as inhibiting bone formation (Redlich and Smolen, 2012).

Pro-inflammatory cytokines, such as TNF, IL-1 and IL-6, enhance osteoclastogenesis, with IL-6 thought to play a particularly important role (Redlich and Smolen, 2012). Macrophage-colony-stimulating factor 1 (M-CSF) and RANKL are critical for osteoclast differentiation and maturation (Redlich and Smolen, 2012, Nakashima et al., 2011). These pro-inflammatory cytokines induce RANKL in cells, thus increasing osteoclastogenesis, as well as inducing differentiation and activation of osteoclasts from the pre-osteoclast level (i.e. from the monocyte-macrophage lineage) independently of RANKL (Devlin et al., 1998, Ma et al., 2004, Kobayashi et al., 2000, Lam et al., 2000).

B and T cells are also important for bone remodelling. Activated T cells are in part responsible for the production of TNF-α and IL6, both of which enhance osteoclastogenesis as outlined above. The discovery that antibodies to citrullinated proteins (ACPA) in RA are associated with worse bone outcomes, including more systemic bone loss (Harre et al., 2012), led to increasing attention on the role B cells play in bone remodelling. Supporting this is the finding that both healthy individuals with ACPA but without a diagnosis of RA, as well as ACPA-positive early arthritis individuals, have bone loss and damage (Kleyer et al., 2014, Llorente et al., 2017), In addition, activated B cells have been shown to express osteoclastogenic factors (Choi et al., 2001).

In chronic inflammation, osteoblast function has been found to be severely impaired, due to the action of pro-inflammatory cytokines (Redlich and Smolen, 2012). Several pro-inflammatory cytokines inhibit osteoblastogenesis, in particular TNF, IL1 and IL6, through different mechanisms; for example, TNF inhibits the osteoblast differentiation factor RUNX2 (Gilbert et al., 2002, Ding et al., 2009, Hughes and Howells, 1993). Activation of NF-kB pathway by cytokines also has an inhibitory effect on osteoblastogenesis (Krum et al., 2010). In addition, TNF induces DKK1, which inhibits the WNT signalling pathway, which is a pivotal pathway in the differentiation and activation of osteoblasts (Redlich and Smolen, 2012). The net result is that systemic chronic inflammation results in overactive osteoclasts along with hypoactive osteoblasts, leading to a profound reduction in bone mass, or osteoporosis.

As well as systemic bone loss, focal articular bone destruction can also occur in inflammatory arthritis. Erosions are a characteristic feature of RA, occurring due to the differentiation and activation of osteoclasts from macrophages within the synovial tissue. The action of the osteoclasts in the synovium is hugely enhanced due to overexpression of RANKL on synovial fibroblasts and infiltrating lymphocytes, in addition to high levels of pro-inflammatory cytokines which amplify the action of osteoclasts and inhibit the action of osteoblasts (Redlich and Smolen, 2012, Goldring et al., 2013). Although RA is the classical inflammatory arthritis associated with erosions, osteoclast focal bone resorption is common to a number of inflammatory arthritidies, including psoriatic arthropathy and axSpA, although the sites affected differ. In contrast, SLE is characterised by a non-erosive arthritis, and analysis of synovial tissues in those individuals reveal an abundance of interferons, which inhibit osteoclast differentiation (Takayanagi et al., 2002, Mensah et al., 2010).

The pattern of bone formation differs substantially between the inflammatory arthritidies. RA, for example, has virtually no bone formation in the untreated state. In contrast, axSpA is characterised by focal increased bone formation at entheseal and spinal sites.

3.4 Pathological bone remodelling in axSpA

Completely understanding the mechanisms behind the structural damage in axSpA remains a challenge, but it is likely that a pathological remodelling process contributes (Magrey and Khan, 2017). The entheses are thought to be the primary site of inflammation in axSpA (Sherlock et al., 2012, McGonagle et al., 2001). Osteitis occurs in the first instance, followed by localised bone loss at the entheses, then excessive bone formation manifesting as new bony protrusions called syndesmophytes (spine) and enthesophytes (peripheral joints) occurs in adjacent periosteal sites

(Goldring, 2013). This new bone formation, or osteoproliferation, can progress, leading to bridging of the intervertebral spaces, facet joints and SI joints, and in extreme cases complete ankylosis of the spine, or a "bamboo" spine (Schett, 2011). This osteoproliferation differentiates axSpA from other forms of inflammatory arthritis.

The pathophysiology behind this process of ankylosis is still incompletely understood. Local biomechanical stress may contribute to the onset of inflammation, as well as the extent of osteophyte formation, and explain why axSpA affects weight-bearing parts of the skeleton predominantly (Jacques et al., 2014). The inflammation that occurs can lead to erosions, which is followed by a repair process, whereby subchondral bone marrow is replaced by fibrosis and granulation tissue (Poddubnyy and Sieper, 2017). This in turn sends out stimuli for syndesmophyte formation, which are added at the margins of vertebral bodies by endochondral ossification (replacement of cartilage by bone), originating from the entheses (Goldring, 2013, Van Mechelen et al., 2018). Syndesmophytes have been shown to be more likely to occur at previously inflamed vertebral edges (Maksymowych et al., 2009, Baraliakos et al., 2014), supporting this link between inflammation and ankylosis.

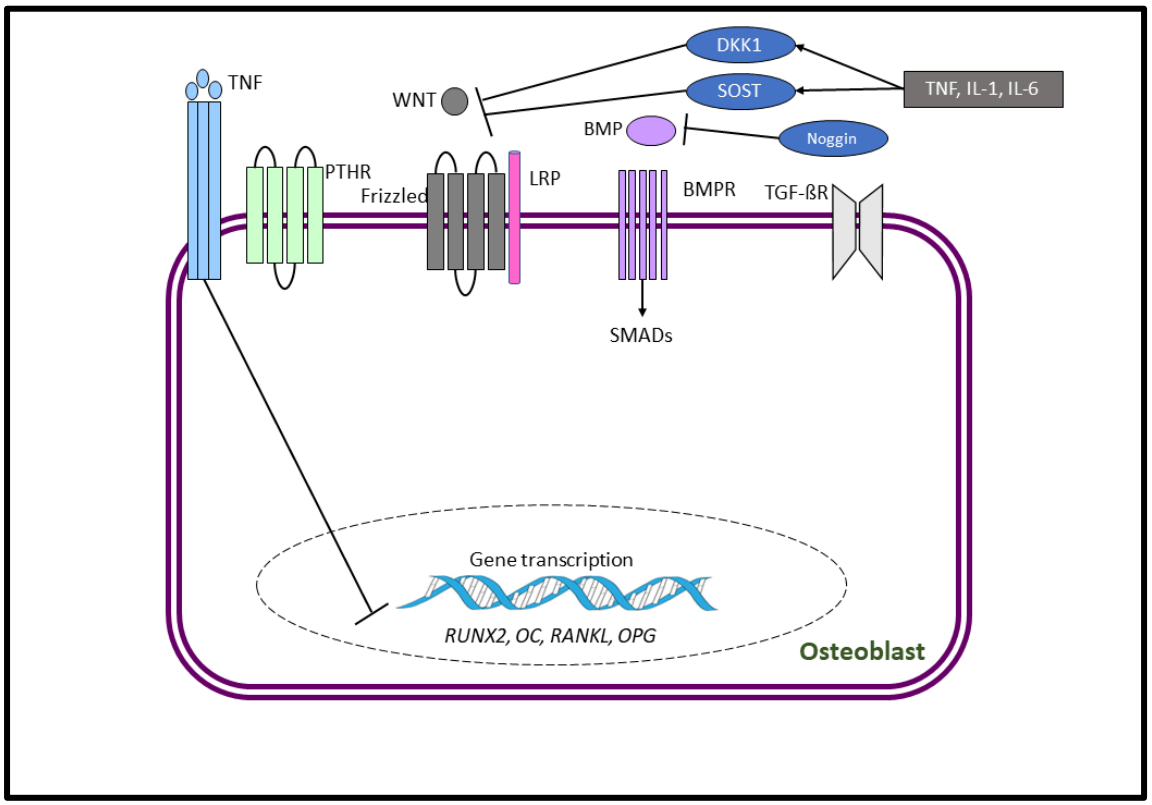
Mouse studies investigating osteophyte and enthesophyte formation suggest that the process of direct bone formation also contributes to ankylosis (Lories et al., 2009). Although evidence from individuals with AS is rare (Appel et al., 2010), the available literature supports the concept that direct bone formation also contributes to ankylosis in AS, in addition to the effect of endochondral ossification (Lories and Haroon, 2017).

Although it is largely accepted that inflammation is important in the ankylosis process, the exact role it plays has been the topic of hot debate, mainly sparked by the early observation that anti-TNF did not affect ankylosis, both in mouse models and cohort studies (Lories et al., 2007, van der Heijde et al., 2009b, van der Heijde et al., 2008). This observation appeared to contradict the hypothesis that inflammation directly stimulates ankylosis. However, a number of mouse models have suggested that inflammation and ankylosis are linked, with inflammation and new bone formation occurring concurrently in some models and in sequence in others (Lories and Haroon, 2017). One exception is a mouse model with overexpression of TNF, where no new bone formation is seen, likely due to the negative effect of TNF on cell differentiation cascades (Jacques et al., 2014). Therefore, it is likely that inflammation and new bone formation are linked, but that the relationship is indirect.

From a molecular perspective, osteoproliferation appears to involve bone morphogenetic proteins (BMP), the Wnt pathway and fibroblast growth factors among others (Sieper and Poddubnyy,

2017). Osteoproliferation in turn can be inhibited by sclerostin and DKK1, as well as noggin, an antagonist of endogenous BMP (Sieper and Poddubnyy, 2017, Lories and Haroon, 2017) (Figure 1-1).

Figure 3-1: Simplified schematic outlining key signalling pathways in osteoblasts during inflammation. Adapted from (Redlich and Smolen, 2012). BMP: bone morphogenetic protein; BMPR: bone morphogenetic protein receptor; DKK: dickkopf-related protein; IL: interleukin; LRP: low-density lipoprotein; OC: osteocalcin; OPG: osteoprotegerin; PTHR: parathyroid hormone receptor; RANKL: Receptor activator of nuclear factor-κß ligand; RUNX: runt-related transcription factor; SOST: sclerostin; TGF: transforming growth factor; TGFR: transforming growth factor receptor; TNF: tumour necrosis factor.



It appears that in SpA trabecular and cortical bone react differently to inflammation: the trabecular bone of the vertebrae is directly exposed to inflammation (osteitis), with subsequent bone loss (or osteoporosis); however, the osteoproliferative changes primarily consist of cortical bone occurring distant to the inflammatory tissue (Schett, 2011, Goldring, 2013). Both IL-17 and TNF have been associated with osteitis on MRI and is strongly associated with trabecular bone loss (Lories and Haroon, 2017).

This co-existence of inflammation-induced bone loss in the vertebra, along with adjacent osteoproliferation which can lead to ankylosis, has been coined the axSpA paradox (Carter and Lories, 2011).

3.5 Epidemiology of osteoporosis in axSpA

In recent times, the body of literature examining BMD and osteoporosis in axSpA has been growing. It is almost universally accepted that individuals with axSpA have a higher prevalence of both osteopenia and osteoporosis, when compared to age- and sex-matched controls. However, it is difficult to accurately characterise the scale of the problem from the available literature, as there is a wide variation in the reported prevalence of low BMD, with figures ranging from 4% to 58% (see Table 3-1). There are many potential reasons for this wide discrepancy in the reported prevalence of low BMD. Firstly, there is a variation in the design of the existing studies, with a mixture of retrospective and prospective analyses. The majority of studies are cross-sectional, reporting point-prevalence, with only a few longitudinal studies. Secondly, different techniques are used in the evaluation of BMD, including DXA and quantitative computed tomography (qCT), with different abilities of these techniques to detect low BMD. A further confounder is the change in classification criteria published by ASAS in 2009 (Rudwaleit et al., 2009c) (see Section 1.3.3): older studies exclusively use individuals with AS, as defined by the modified New York (mNY) criteria, whereas newer ones use a combination of axSpA and AS individuals. All these factors make it difficult to compare the existing literature accurately, thus limiting our understanding of the scale of the problem.

The literature is almost universal in agreeing that individuals with advanced or established axSpA have a higher prevalence of low BMD than controls (see Table 3-1). However, low BMD is not a complication that is restricted to late disease. BMD has been shown to decline early in the axSpA disease process, with low BMD demonstrated in over 50% of axSpA individuals within the first decade of diagnosis (van der Weijden et al., 2012). In addition, Forien et al demonstrated that the presence of low BMD, which they defined as a T score of $\leq$ -2, had good predictive value

(positive likelihood ratio of 2.6-3.1) in diagnosing axSpA in individuals with suggestive symptoms (Forien et al., 2015). Akgol et al additionally reported that individuals with non-radiographic (nr) axSpA had significantly lower lumbar spine BMD than individuals with mechanical lower back pain (Akgol et al., 2014).

Therefore, we can conclude that osteoporosis occurs at an increased prevalence in axSpA, beginning early in the disease process. However, just how common osteoporosis actually is in axSpA is not clear.

Table 3-1: Summary of studies outlining the prevalence of low bone mineral density in axial spondyloarthritis.

Author	Design	Study population	N (M/F)	Disease duration, years (mean)	BMD measurement technique(s)	Result
(Akgol et al., 2014)	Cross-sectional	LBP[$]	46 (32/14)	1.25	DXA: AP LS, FN	LS BMD lower in nr-axSpA than mLBP patients. Low BMD associated with spinal inflammation on MRI (LS, FN).
(Arends et al., 2011)	Cross-sectional	AS[†]	128 (93/35)	14	DXA: AP LS, TH	57% had LS or TH BMD T score ≤ -1. Difference between LS and TH BMD positively correlated with disease duration.
(Briot et al., 2013)	Cross-sectional	IBP[††] *(axSpA criteria: 71.4%)*	332 (174/158)	M: 1.6 F: 1.7	DXA: LS, TH, FN	Low BMD: 11.5% LS, 4.2% hip, 13% both sites. LS BMD significantly lower in patients with BMO. Lower BMD (LS, TH) in patients fulfilling ASAS criteria.
(Capaci et al., 2003)	Cross-sectional	AS[†]	73 (49/24)	11.8	DXA: AP LS, TH	Mild AS: low BMD 68.4% at LS, 51.9% TH. Advanced AS: low BMD 54.3% at LS, 91.7% TH. LS BMD similar in mild and advanced AS. Prevalence of TH osteoporosis higher in patients with advanced AS.
(Devogelaer et al., 1992)	Cross-sectional	AS[†]	70 (60/10)	15.4	SPA: radius DXA: LS SEQCT: LS	DXA LS BMD significantly lower in patients than controls. QCT: BMD lower in patients than controls.
(Donnelly et al., 1994)	Cross-sectional	AS[#]	87 (62/25)	M: 16.3 F: 16.6	DXA: AP LS, FN, WB	LS BMD significantly lower in M than F. BMD reduced in LS and FN in early disease. LS BMD increased in late disease. FN BMD further decreased in late disease.
(El Maghraoui et al., 2005)	Cross-sectional	AS[†]	43 (43/0)	6.8	QCT: LS	Mean LS BMD significantly lower in AS patients than controls.

Author	Design	Study population	N (M/F)	Disease duration, years (mean)	BMD measurement technique(s)	Result
(Forien et al., 2015)	Cross-sectional	AxSpA[††] *axSpA n=193* *nr-axSpA n=61*	193 (122/71)	11.2	DXA: AP LS, FN, TH	Prevalence of low BMD: 26.4% (LS), 13.6% (TH), 40.3% (at least 1 site). Nr-axSpA: LS BMD lower than controls (T score ≤ -2 in 28.1% v 9.7%, p=0.01). LR+ of low BMD for axSpA diagnosis: 2.6 (LS), 3.12 (TF). LR+ of low BMD for nr-axSpA diagnosis: 2.9 (LS), 2.54 (TF).
(Geusens et al., 2015)	Cross-sectional	SpA[‡] *73.3% AS,* *10.3% PsA,* *4.6% EnA,* *11.8% uSpA*	390 (175/215)	10.8	DXA: AP LS, FN, TH	T score ≥ -1: 79.7% (LS), 59.5% (FN). T score between -1 and -2.5: 17.2% (LS), 36.4% FN. T score ≤ -2.5: 3.1% (LS), 4.1% (FN).
(Ghozlani et al., 2009)	Cross-sectional	AS[†]	80 (67/13)	10.8	DXA: AP LS, FN, TH	Prevalence of osteoporosis at any site: 25%
(Gratacos et al., 1999)	Longitudinal *mean follow-up 19 months*	AS[‡‡]	34 (27/7)	Active AS: 7.5 Inactive AS: 5.3	DXA: AP LS, FN	Active AS had significant bone mass loss at LS (5%) and FN (3%).
(Grazio et al., 2012)	Cross-sectional	AS[†]	80 (46/34)	21.8	DXA: AP LS, TH, FN	Osteopenic: 20% LS, 26.2% TH, 47.5% FN. Osteoporotic: 25% LS, 7.5% TH, 22.5% FN. Significantly more patients osteoporotic at LS than TH.
(Nigil Haroon et al., 2015)	Cross-sectional	AS[†]	53 (29/24)	17	DXA: AP LS, FN, TH HRpQCT: distal radius and tibia	Osteopenia: 34% (M: 31%, F: 38%). Osteoporosis: 11% (M: 10%, F: 13%). vBMD lower at distal radius & tibia in AS than controls.
(Jun et al., 2006)	Cross-sectional	AS[†]	68 (68/0)	68 mo	DXA: PA LS, TH, FN	Lower BMD in AS patients (LS, TH, FN) than controls.

Author	Design	Study population	N (M/F)	Disease duration, years (mean)	BMD measurement technique(s)	Result
(Karberg et al., 2005)	Cross-sectional	AS†	103 (66/37)	I (≤ 5 years): 2.5 II (5-10 years): 7 III (>10 years): 19.7	DXA: AP LS, FN DEQCT: LS pQCT: radius	Prevalence (%) of osteopenia and osteoporosis at each site: DXA LS: 31, 14 DEQCT LS: 44, 11 DXA FN: 52, 24 pQCT radius: 16, 1. DXA FN classified more osteoporosis than DXA LS or DEQCT in longer disease. DEQCT classified increasing % of patients as osteoporosis with increasing disease duration, DXA LS was the opposite.
(Klingberg et al., 2013)	Cross-sectional	AS†	69 (69/0)	23	DXA: AP LS, lat LS, FN, TH, radius QCT: LS HRpQCT: radius and tibia	vBMD lower in AS than controls by HRpQCT (radius/tibia). Prevalence (%) of osteopenia and osteoporosis at LS: AP DXA: 19, 6 QCT: 30, 38
(Klingberg et al., 2012c)	Cross-sectional	AS†	204 (117/87)	24	DXA: AP LS, lat LS, FN, TH, radius	≥ 50 years: osteopenia 43.6%, osteoporosis 20.8%. < 50 years: 4.9% low BMD. LS most common location for low BMD, followed by radius, then FN. Lat LS significantly lower than AP LS BMD.
(Korkosz et al., 2011)	Longitudinal *10-year follow-up*	AS†	15 (15/0)	16.5	DXA: AP LS, TH, FN SE-QCT: LS	QCT baseline: n=5 osteopenia, n=6 osteoporosis. Significant decrease in BMD in LS by QCT over 10 years. DXA LS: increased BMD. FN/TH: no significant change in BMD. No correlation between QCT and DXA.

Author	Design	Study population	N (M/F)	Disease duration, years (mean)	BMD measurement technique(s)	Result
(Lange et al., 2005a)	Cross-sectional	AS†	84 (53/31)	I: 9 II: 20 III: 21 IV: 32	DXA: AP LS, TH SE-QCT: LS	DXA: osteopenia in 5% and osteoporosis in 9.2%. SE-QCT: osteopenia 11.8%, osteoporosis 30.3%.
(Maillefert et al., 2001)	Longitudinal *2-year follow-up*	AS†	54 (35/19)	12.4	DXA: PA LS, FN	Baseline: FN - 39% osteopenic and 11% osteoporotic; LS – 39% osteopenic, 17% osteoporotic. Follow-up: significant bone loss at FN, not at LS; no significant change in proportion of osteopenic and osteoporotic patients.
(Mitra et al., 2000)	Cross-sectional	AS¥	66 (66/0)	9.85	DXA: AP LS, FN	Reduced BMD (LS, FN) in AS compared to controls.
(Toussirot et al., 2001)	Cross-sectional	AS†	71 (49/22)	10.6	DXA: AP LS, FN	Prevalence (%) of normal BMD, osteopenia and osteoporosis at each site: LS: 53.5, 32.4, 14.1 FN: 73.2, 22.5, 4.3
(Ulu et al., 2014)	Cross-sectional	AS†	59 (50/9)	11.5	DXA: PA LS, lat LS, TH	PA LS: osteopenia 51%, osteoporosis 15%. FN: osteopenia 46%, osteoporosis 12%. Lat LS ≤ T score -2.5: 32%.
(Ulu et al., 2013)	Cross-sectional	AS†	86 (69/17)	11.74	DXA: PA LS, lat LS, TF, FN	Comparison with control group: FN, TF & lat LS significantly lower in AS patients. No significant difference in PA LS between groups. PA LS significantly higher in late versus early AS.
(van der Weijden et al., 2011)	Cross-sectional	SpA¥¥ + IBP *AS 72%* *uSpA 12%* *PsA 8%* *IBD 4%* *ReA 4%*	130 (86/44)	6.3	DXA: AP LS, PF	Prevalence of low BMD: Osteopenia 28.5% (FN), 30.8% (LS), 37.7% (both) Osteoporosis 2.3% (FN), 7.7% (LS), 8.5% (both). No significant differences in BMD between hip and LS.

Author	Design	Study population	N (M/F)	Disease duration, years (mean)	BMD measurement technique(s)	Result
(Venceviciene et al., 2015)	Longitudinal *48-month follow-up*	SpA[¥¥] *AS 51%* *PsA 27%* *EnA 10%* *ReA 12%*	41 (34/7)	62.2 months	DXA: PF	27% of patients had BMD loss over the 48 months.

#: classification criteria for inclusion not reported; [$]: chronic lower back pain (LBP), divided into 2 groups – 1. fulfil ASAS criteria 2.mechanical LBP; †: fulfilling modified New York (mNY) criteria; ††: symptoms suggestive of axSpA according to local rheumatologist's assessment; ‡: SpA diagnosis made by treating rheumatologist; ‡‡: < 10 years duration, no ankylosis, persistent inflammatory disease activity; ¥: modified Schober's test ≥ 5cm, radiographically normal hips, absent or incipient syndesmophytes; ¥¥: ESSG criteria; AP: anteroposterior; AS: ankylosing spondylitis; ASAS: Assessment of SpondyloArthritis International Society; axSpA: axial spondyloarthropathy; BMD: bone mineral density; BMO: bone marrow oedema; DEQCT: dual-energy quantitative computed tomography; DXA: dual-energy x-ray absorptiometry; EnA: enteropathic arthropathy; F: female; FN: femoral neck; HRpQCT: high-resolution peripheral quantitative computed tomography; IBP: inflammatory back pain; lat LS: lateral lumbar spine; LR+: positive likelihood ratio; LS: lumbar spine; M: males; mLBP: mechanical lower back pain; nr-axSpA: non-radiographic axial spondyloarthritis; NR: not reported; PA: posterioanterior; PF: proximal femur; pQCT: peripheral quantitative computed tomography; PsA: psoriatic arthropathy; ReA: reactive arthritis; SEQCT: single-energy QCT; SpA: spondyloarthropathy; SPA: single-photon absorptiometry; TH: total hip; uSpA: undifferentiated SpA; vBMD: volumetric bone mineral density; WB: whole body.

3.6 Factors associated with osteoporosis in axSpA

The risk factors for reduced BMD are well outlined in the general population and include increasing age, postmenopausal status and female sex among others (Compston et al., 2019). Robust evidence supporting patient and disease characteristics associated with bone loss in axSpA is lacking, in large part due to a limited number of studies investigating this (see Table 3-2).

3.6.1 Gender

In the general population, females are known to have a higher risk of osteoporosis than men (Johnell and Kanis, 2006). In axSpA, a systematic review examining the prevalence and risk factors for osteoporosis and fractures showed that more men than women have osteoporosis (Ramirez et al., 2018). However, there were more men than women in all of the studies included in the systematic review, with some studies exclusively recruiting men. This apparent gender effect may represent a bias owing to the historic under-recognition of axSpA in females and subsequent under-representation in studies. As this disease is increasingly diagnosed in women, more robust studies with equal gender spread may answer this question more definitively. However, as the existing literature has an excess of men, it highlights that low BMD does indeed affect males with axSpA, a critically important point to take note of, as men and osteoporosis are not often thought of in the same sentence.

3.6.2 Disease duration

In most chronic inflammatory conditions, bone loss or osteopenia is an inevitable consequence (Straub et al., 2015). In keeping with this theory of chronic inflammation inducing osteopenia (Straub et al., 2015, Redlich and Smolen, 2012), BMD loss is known to begin early in the disease course of both nr-axSpA and AS (Capaci et al., 2003, van der Weijden et al., 2011, Akgol et al., 2014). However, increasing disease duration is not consistently associated with worsening BMD, with BMD of the spine often increasing with more established disease when assessed using conventional DXA (see Table 3-2). Another feature noted when exploring the effect of disease duration on BMD in axSpA is that the difference between PA lumbar spine and hip T scores measured by DXA increases in tandem with disease duration (Arends et al., 2011). However, lateral DXA measurements appear to correlate better with disease duration (Ulu et al., 2013). Potential reasons for these conflicting findings are discussed later in Section 3-8.

3.6.3 Disease severity

One of the most frequently used tools to assess disease activity is the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), a patient-reported outcome (PRO) (Garrett et al., 1994). Many DXA studies have found no correlation between BMD and BASDAI (Klingberg et al., 2012c, Gratacos et al., 1999, Briot et al., 2013). However, a cross-sectional qCT study measured BMD of the lumbar spine and found a higher BASDAI in individuals with osteoporosis of the spine than without (8 versus 4, $p<0.05$) (Lange et al., 2005b). In contrast, Arends et al (Arends et al., 2011) found that when AS individuals were categorised as low BMD (T score of the lumbar spine or hip $\leq$-1 by DXA), a lower BASDAI was independently associated with low BMD (hip or spine).

A disadvantage of BASDAI is that it reflects the current disease activity and doesn't capture periods of potentially prolonged active disease in the past. Therefore, it is possible that a once-off calculation of BASDAI can't predict BMD loss, but that the average score over time would be more useful. This hypothesis is supported by a four-year longitudinal DXA study of SpA individuals (Venceviciene et al., 2015), where the patient group with more BMD loss had a higher average BASDAI score than those without BMD loss.

The Bath Ankylosing Spondylitis Metrology Index (BASMI) is a validated tool to objectively assess spinal mobility (Jenkinson et al., 1994). A number of studies have found an association between higher BASMI (total score or components) and low BMD (Donnelly et al., 1994, El Maghraoui et al., 2005, Ulu et al., 2014, van der Weijden et al., 2011, Venceviciene et al., 2015) (see Table 3-2).

Many studies (see Table 3-2), both longitudinal and cross-sectional, including DXA and QCT, have found an association between higher CRP or ESR and lower BMD (Briot et al., 2013, Ghozlani et al., 2009, Gratacos et al., 1999, Maillefert et al., 2001, Venceviciene et al., 2015, Jun et al., 2006, Klingberg et al., 2012c). Whether the addition of laboratory parameters to PROs in scores such as the ankylosing spondylitis disease activity score (ASDAS) improves the predictive value of low BMD doesn't appear to have been investigated.

From the Outcome in AS International Study (OASIS) cohort (Ramiro et al., 2014), we know that more active disease is associated with progressive radiographic spinal change, which can be scored using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). In the presence of syndesmophytes, more AS individuals had low BMD when measured by DXA of femoral neck or DEQCT of lumbar than when AP DXA of the spine was used (Karberg et al., 2005). After ten

years of disease duration, AP DXA of the lumbar spine did not detect any cases of osteoporosis and DEQCT at lumbar spine and DXA of femoral neck were used instead. Another study using quantitative computed tomography (QCT) to assess BMD of the lumbar spine showed that increasing mSASSS correlated significantly with a lower volumetric BMD in the lumbar spine (Klingberg et al., 2013). In this study, peripheral bone microarchitecture, as measured by high resolution peripheral quantitative computed tomography (HRpQCT) of the radius and tibia, was also worse in individuals with more advanced structural damage, a finding supported by Haroon et al (Nigil Haroon et al., 2015).

Therefore, on balance, the evidence supports the theory that more severe disease is associated with lower BMD. However, the method used to assess BMD may influence our ability to detect low BMD.

3.6.4 Other risk factors

Many of the traditional risk factors for osteoporosis have not been investigated in axSpA, including low physical activity, falls, dementia, hypercalciuria and living in residence (Ramirez et al., 2018).

3.7 Systemic or local process

An early theory proposed was that osteoporosis of the spine in AS was due to local inflammation and spinal immobility, with peripheral sites largely spared. However, the literature is conflicting as to whether BMD loss in axSpA is a local or systemic process, with no clear consensus. Low BMD was significantly more common in 103 AS individuals at femoral neck than at the lumbar spine measured by DXA or dual-energy quantitative computed-tomography (DEQCT) (Karberg et al., 2005). However, another study of 71 AS individuals with a mean disease duration of 10.6 years found that the prevalence of low BMD was higher than controls at the lumbar spine, but not the femoral neck (Toussirot et al., 2001). Yet other DXA studies have shown the central and peripheral skeletons are equally affected by low BMD (Klingberg et al., 2012c). It is difficult to adequately compare these studies, due to the difference in populations and BMD measurement techniques.

Table 3-2: Summary of studies detailing factors associated with low BMD in axial spondyloarthritis. Study methodology is outlined in Table 3-1.

Author	Age	Sex	mSASSS	BASMI	BASDAI	Disease duration	CRP	ESR	Other
(Akgol et al., 2014)									BMO on MRI associated with lower BMD at spine and hip (DXA)
(Arends et al., 2011)	NS	Male sex associated with lower BMD* (DXA)			Lower BASDAI associated with lower BMD* (DXA)	NS	NS	NS	
(Briot et al., 2013)	NS	Male sex associated with lower BMD at spine & hip (DXA)		NS	NS	NS	Higher CRP associated with low BMD at spine (DXA)	Higher ESR associated with low BMD at spine (DXA)	BMO on MRI associated with lower BMD at spine and hip (DXA)
(Capaci et al., 2003)						Longer duration correlated with higher BMD at spine and lower BMD at hip (DXA)			
(Donnelly et al., 1994)		Male sex associated with lower BMD at spine (DXA)		Low Schobers associated with reducing BMD at hip and increasing BMD at spine (DXA)					
(El Maghraoui et al., 2005)	Increasing age associated with lower BMD at spine (QCT)			Increasing BASMI associated with lower BMD at spine (QCT)	NS	Longer disease duration associated with lower BMD at spine (QCT)		NS	
(Forien et al., 2015)			mSASSS >0 vs mSASSS=0: higher BMD at spine, but lower at hip (DXA)						

Author	Age	Sex	mSASSS	BASMI	BASDAI	Disease duration	CRP	ESR	Other
(Ghozlani et al., 2009)	NS		NS	NS	Higher BASDAI associated with osteoporosis* (DXA)	Longer disease duration associated with osteoporosis* (DXA)	Higher CRP in patients with osteoporosis* (DXA)	Higher ESR in patients with osteoporosis* (DXA)	
(Gratacos et al., 1999)							Higher CRP associated with lower BMD* (DXA)	Higher ESR associated with lower BMD* (DXA)	
(Grazio et al., 2012)	NS				Higher BASDAI associated with lower BMD at LS (DXA)	NS	Higher CRP associated with lower BMD at LS & hip (DXA)	Higher ESR associated with lower BMD at LS & hip (DXA)	
(Jun et al., 2006)							Higher CRP associated with lower BMD at LS (DXA)	Higher ESR associated with lower BMD at LS (DXA)	
(Karberg et al., 2005)	Increasing age associated with lower BMD at LS (DEQCT)		Syndesmophytes a/w osteoporosis (FN: DXA; LS: DEQCT)		NS	NS	NS		
(Klingberg et al., 2013)			Increasing mSASSS associated with lower BMD at LS (QCT)						
(Klingberg et al., 2012c)	Increasing age associated with lower BMD at LS, hip & radius (DXA)	Osteoporosis and osteopenia at spine more common in women (DXA)	Increasing mSASSS associated with lower BMD at LS & FN (DXA)	NS	Increasing BASDAI associated with lower BMD at spine, hip & radius (DXA)	Longer disease duration associated with lower BMD at hip & spine (DXA)	Increasing CRP associated with lower BMD at LS (DXA)	Increasing ESR associated with lower BMD at LS, hip & radius (DXA)	
(Korkosz et al., 2011)	NS		NS			NS		NS	

Author	Age	Sex	mSASSS	BASMI	BASDAI	Disease duration	CRP	ESR	Other
(Maillefert et al., 2001)	NS	NS		NS	NS	NS	NS	Increasing ESR associated with lower BMD at hip (DXA)	
(Mitra et al., 2000)						NS			
(Toussirot et al., 2001)					NS	Increasing disease duration associated with lower BMD at hip (DXA)	NS	NS	
(Ulu et al., 2014)	NS	NS		Higher BASMI associated with lower BMD at spine (DXA)	NS	Increasing disease duration associated with higher BMD at PA spine and lower BMD at lateral spine (DXA)	NS	Increasing ESR associated with lower BMD at lateral LS (DXA)	
(Ulu et al., 2013)						Increasing disease duration associated with higher BMD at PA spine and lower BMD at lateral spine (DXA)			
(van der Weijden et al., 2011)	NS	Male sex associated with low BMD* (DXA)		Higher BASMI associated with lower BMD (DXA)*	NS	NS	Increased CRP associated with lower BMD (DXA)*	NS	
(Venceviciene et al., 2015)	NS	NS		Higher components of BASMI associated with lower BMD (lateral flexion, IM distance)	Higher average scores of BASDAI over 4 years associated with lower BMD at hip (DXA)	NS	Higher CRP associated with lower BMD at hip (DXA)	Higher ESR associated with lower BMD at hip (DXA)	

Author	Age	Sex	mSASSS	BASMI	BASDAI	Disease duration	CRP	ESR	Other

**: BMD site of correlation not reported; blank cell: variable not reported in study.*

A/w: associated with; BASDAI: Bath Ankylosing Spondylitis Disease Activity; BASMI: Bath Ankylosing Spondylitis Metrology Index; BMD: bone mineral density; BMO: bone marrow oedema; CI: confidence interval; CRP: C reactive protein; DEQCT: dual energy quantitative computed tomography; DXA: dual-energy x-ray absorptiometry; ESR: erythrocyte sedimentation rate; IM: intermalleolar distance; LS: lumbar spine; MRI: magnetic resonance imaging; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; NS: not significant, p>0.05; OR: odds ratio; QCT: quantitative computed tomography; vs: versus.

3.8 Fractures in axSpA

The clinical significance of osteoporosis is in the increased risk of fractures. In the general population, this risk is well outlined (Johnell and Kanis, 2006). Multiple studies have shown that individuals with AS have an increased risk of vertebral fractures (VF) compared to age- and sex-matched controls (Donnelly et al., 1994, Mitra et al., 2000, Pray et al., 2017, Vosse et al., 2009). It is also known that VF that occur in the context of axSpA have a higher rate of complications, including devastating neurological outcomes (Westerveld et al., 2009), than the general population. There is therefore a clinical need to understand the reason for this excess risk.

Studies have demonstrated a wide variation in the reported prevalence figures of VF in axSpA, with figures ranging from 1.4% to 39% (see Table 3-3). A large primary care-based case-control study in the United Kingdom (UK) (Vosse et al., 2009) selected 231,436 cases of fracture, vertebral and non-vertebral, recorded in the General Practice Research Database (GPRD) and matched with 231,362 controls. AS individuals had an increased risk of clinical VF than controls, even when corrected for potential confounders (OR 3.26, 95% CI 1.51-7.02). However, the risk of peripheral fractures in individuals with AS was not increased, except in a subset that had a concomitant diagnosis of IBD (OR 2.79, 95% CI 1.10 to 7.08). A Swedish-based registry study (Robinson et al., 2013) identified all individuals with a primary discharge diagnosis of VF and concomitant diagnosis of AS admitted between 1987 and 2008 and demonstrated a prevalence of 4.1% for clinical VF amongst AS participants, with the proportion of fractures increasing throughout the 22 years. Registry-based data may underestimate the true prevalence of VF as they don't always come to clinical attention (Klingberg et al., 2012b) and prevalence on x-ray studies has shown to be much higher (Table 3-3).

A systematic review and meta-analysis examined the effects of AS on vertebral fractures and confirmed that the risk of vertebral fractures is almost doubled for AS individuals, compared to non-AS controls (OR 1.96, 95% CI 1.52 to 2.51) (Pray et al., 2017). The authors of this study, Pray et al, also investigated the risk factors for VF in axSpA and found lower BMD of the femoral neck, total hip and distal radius in individuals with VF compared to those without (Pray et al., 2017). However, the authors found no difference in lumbar spine BMD in AS participants with and without VF (Pray et al., 2017). Other clinical factors identified in this analysis as associated with VF in AS included increasing age, male sex, longer disease duration, mSASSS and BASRI (Pray et al., 2017). Pray et al also reported that the risk of non-vertebral fractures in AS was increased (OR 1.10, 95% CI 1.04 to 1.15), but not hip fractures (OR 1.17, 95% CI 0.71 to 1.92). However, there were only a small number of studies identified that reported this and were suitable for inclusion in the systematic review.

A more recent meta-analysis confirmed that the risk of osteoporotic fractures is higher in axSpA individuals than controls (OR 23.7, 95% CI 6.4 to 87.2) (Ramirez et al., 2018). In addition, individuals with fractures were reported to have a significantly higher BASRI than individuals without; however, there was high heterogeneity between the studies (I^2=91%, p<0.001), prohibiting interpretation of the presented meta-analysis results. Data on the relationship between BMD and fractures is not presented in this review and no information is given on how they decided to consider a fracture as osteoporotic versus non-osteoporotic (Ramirez et al., 2018).

Decreased bone strength may play a role in accounting for the excess risk of vertebral fractures in axSpA. HRpQCT of the distal radius and tibia demonstrated that AS individuals had worse microarchitecture (lower cortical and total vBMD, reduced cortical thickness, increased cortical porosity) than non-AS individuals, despite there being no difference in BMD by DXA between groups at either the radius or lumbar spine (Nigil Haroon et al., 2015). In another study, male AS individuals with VF demonstrated significantly worse peripheral bone microarchitecture as measured by HRpQCT of the distal radius and ulna than AS individuals without a VF (Klingberg et al., 2013).

Interpretation of the existing literature can confidently conclude that the risk of fractures, particularly vertebral fractures, is increased in individuals with axSpA. More research is needed to investigate the reason for the increased risk of VF, considering the lack of association between lumbar spine BMD and VF, yet lower hip BMD in those with VF, along with the relationship between structure damage (mSASSS and BASRI) and VF. The excess risk of VF in this population is likely multifactorial.

Table 3-3: Summary of studies outlining the prevalence of vertebral fractures in axial spondyloarthritis.

Author	Design	N (M/F)	Study population	Disease duration, years (mean)	Definition of VF	Prevalence of VF (%)	Association with low BMD
(Arends et al., 2011)	Cross-sectional	128 (93/35)	AS[†]	14	Radiographic[A]	20%	No association
(Capaci et al., 2003)	Cross-sectional	73 (49/24)	AS[†]	11.8	Radiographic[B]	5.5%	No association
(Donnelly et al., 1994)	Cross-sectional	87 (62/25)	AS[#]	M: 16.3 F: 16.6	Radiographic[B]	10.3 (n=9)	No reduction in BMD by DXA of LS, FN and WB.
(Geusens et al., 2015)	Cross-sectional	390 (175/215)	SpA[‡] *(73.3% AS, 10.3% PsA, 4.6% EnA, 11.8% uSpA)*	10.8	Radiographic[A]	11.8%	Significantly associated with FN BMD: OR 1.38 per 1 SD decrease of T score (95% CI 1.08-1.62)
(Ghozlani et al., 2009)	Cross-sectional	80 (67/13)	AS[†]	10.8	Radiographic[A]	18.8%	Associated with reduced BMD and T-score at hip site and presence of osteoporosis at any site
(Jun et al., 2006)	Cross-sectional	68 (68/0)	AS[†]	68 mo	Radiographic[A]	16.2%	Lower BMD at hip
(Klingberg et al., 2012c)	Cross-sectional	204 (117/87)	AS[†]	24	Radiographic[A]	11.8%	Patients with VF had significantly lower BMD at all sites compared to patients without a VF

Author	Design	N (M/F)	Study population	Disease duration, years (mean)	Definition of VF	Prevalence of VF (%)	Association with low BMD
(Klingberg et al., 2013)	Cross-sectional	69 (69/0)	AS[†]	23	Radiographic[A]	12%	DXA: AP and lateral lumbar BMD, lumbar vBMD and BMD of FN and TH all lower in patients with VF. No difference in forearm DXA. QCT: lower cortical lumbar vBMD in presence of VF
(Lange et al., 2005b)	Cross-sectional	58 (38/20)	AS[†]	17.6	Radiographic[C]	12.1%	All VF had osteoporosis by QCT LS
(Maillefert et al., 2001)	Longitudinal *(2-year follow-up)*	54 (35/19)	AS[†]	12.4	Radiographic[A]	3.7%	NR
(Mitra et al., 2000)	Cross-sectional	66 (66/0)	AS[¥]	9.85	Radiographic[B]	16.7% versus 2.6% of controls (OR 5.92)	No correlation between BMD of LS or FN and VF
(Montala et al., 2011)	Cross-sectional	176 (138/38)	AS[†]	22.5	Radiographic[A]	32.4%	NR
(Robinson et al., 2013)	Prospective	17764 (M/F NR)	AS[††]	NR	Clinical[D]	4.1% (n=724) Increased from 0.82% in 1987 up to 11.3% in 2008	NR

Author	Design	N (M/F)	Study population	Disease duration, years (mean)	Definition of VF	Prevalence of VF (%)	Association with low BMD
(Toussirot et al., 2001)	Cross-sectional	71 (49/22)	AS†	10.6	Radiographic[A]	1.4%	NR
(Ulu et al., 2014)	Cross-sectional	59 (28/12)	AS†	11.5	Radiographic[E]	30.6%	VF associated with osteoporosis by lat LS DXA
(Vosse et al., 2009)	Case-control	758 (442/316)	AS†	NR	Clinical[G]	4.5%	NR

†: fulfilling modified New York (mNY) criteria; ‡: SpA diagnosis made by treating rheumatologist; ¥: modified Schober's test ≥ 5cm, radiographically normal hips, absent or incipient syndesmophytes; ††: ICD code of AS in Swedish National Hospital Discharge Registry.

A: morphometric VF on x-rays, Genant[42] classification; B: morphometric VF on x-rays, McCloskey[43] classification; C: morphometric VF on x-rays, vertebral height (thoracic/lumbar spine) height decrease>15%; D: discharge diagnosis; E: morphometric VF on x-rays, vertebral height (thoracic/lumbar spine) height decrease>20%.

AS: ankylosing spondylitis; BMD: bone mineral density; CI: confidence interval; CS: cervical spine; DXA: dual-energy x-ray absorptiometry; F: female; FN: femoral neck; G: VF diagnosis in General Practice Research Database, computerised records of sample of general practitioners in the United Kingdom; LS: lumbar spine; M: male; NR: not reported; OR: odds ratio; QCT: quantitative computed tomography; SD: standard deviation; SpA: spondyloarthropathy; TH: total hip; TS: thoracic spine; VF: vertebral fracture; VH$^{t/l}$: vertebral height (thoracic/lumbar spine); WB: whole body.

3.9 Difficulties with assessing BMD in axSpA

Currently, the gold standard for assessing BMD is posterioanterior (PA) dual-energy x-ray absorptiometry (DXA) at the spine and hip, as recommended by the International Society of Clinical Densitometry (ISCD) (Schousboe et al., 2013). When considering the utility of using PA DXA to assess BMD of the spine in axSpA, we need to recall the inherent pathophysiology of axSpA. As outlined in section 3.3, the osteoproliferation of the spine that occurs in axSpA is dominated by cortical bone. However, it is trabecular bone, which forms the majority of the vertebral body, that is particularly affected in bone loss (Seeman and Delmas, 2006); therefore, it is important that whatever method we use to assess BMD of the spine has the ability to assess the trabecular bone accurately. There is a risk that the extensive cortical-rich osteoproliferation that occurs in the spine can falsely raise the BMD when PA (conventional) DXA is used, giving an illusion of reassuringly normal BMD, even in cases where osteoporosis may be present.

Capaci et al illustrated this potential problem in a study of 73 AS patients, where using PA DXA the authors found that the frequency of low BMD in mild patients was 68% in the lumbar spine, but the prevalence was only 54% in advanced patients (Capaci et al., 2003). This contrasted with the hip, where the prevalence of low BMD increased from 52% in mild patients to 92% in advanced cases. As the duration of axSpA increased, there was a decline of total hip BMD, as would be expected, but this was accompanied by a paradoxical rise in lumbar spine BMD. The authors hypothesised that osteoproliferation was responsible for this finding.

The optimal method to identify BMD loss in axSpA is under dispute. In view of the limitations of traditional PA DXA, a technique which preferentially examines the trabecular bone of the spine is desirable. Quantitative computed tomography (QCT) has the advantage of measuring volumetric BMD (vBMD), without being affected by cortical artefacts, a technique that is highly attractive for AS patients. In a study of 69 AS patients, investigators found that QCT of the lumbar spine detected significantly more cases of osteoporosis and osteopenia than PA DXA (Klingberg et al., 2013). HRpQCT, a newer technique which provides knowledge about bone microarchitecture, was also performed (Klingberg et al., 2013). This demonstrated lower volumetric BMD (vBMD) in the distal radius and tibia of AS patients than in controls. It also demonstrated strong correlations between central and peripheral trabecular vBMD (Klingberg et al., 2013), suggesting a systemic pattern of bone loss.

Although QCT of the lumbar spine has advantages over PA DXA, the radiation dose associated with it makes it unsuitable as a routine screening tool; thus, safer methods are necessary. Lateral DXA scanning of the lumbar spine exclusively examines the BMD of the trabecular component

of the body of the vertebra, thus excluding the cortical-rich posterior components of the spine (Finkelstein et al., 1994, Zmuda et al., 2000). As osteoproliferation predominantly affects the cortical aspect of the spine, lateral DXA should, in theory, be less affected by the changes which occur in the spine of axSpA patients. Similar to axSpA, the degenerative changes that occur in the spine with age in the general population can also overestimate BMD using PA DXA. Lateral DXA has been shown to identify more patients with age-related bone loss than AP DXA, in both men and women (Finkelstein et al., 1994).

When lateral DXA was first introduced, it was performed with the patient lying on their side. However, precision was very low and was deemed too insensitive to have any clinical use. The modern method to acquire lateral DXA scans is that the arm of the DXA scan is rotated 90 degrees and is obtained without the patient moving. Supine lateral measurements have been shown to offer similar precision to the standard PA DXA scan (Blake et al., 1994).

In AS, lumbar spine BMD was significantly lower with lateral DXA measurement than with PA projection (Klingberg et al., 2012c). Therefore, lateral DXA is a promising tool to identify bone loss without being affected by the osteoproliferation associated with axSpA. However, previous studies investigating the use of lateral DXA in axSpA have been limited by lack of reference databases, prohibiting calculation of T-scores.

Trabecular bone score (TBS) is a recently emerged tool which is obtained by re-analysing AP lumbar spine DXA images and evaluating variations in grey-level texture from pixel to pixel. It can distinguish between different microarchitectures that have the same bone density. The higher the TBS, the stronger the microarchitecture of the bone, which in turn is more resistant to fracture. In the general population, TBS is related to fracture risk (Harvey et al., 2015). There is a paucity of literature in axial SpA, but Wildberger et al demonstrated that TBS was not influenced by syndesmophytes, in contrast to PA DXA measurement of the spine, although it did not identify prevalent fractures (Wildberger et al., 2016). Kang et al (Kang et al., 2018) found that TBS was significantly lower in patients with vertebral fractures than those without (mean 1.39 (SD 0.11) versus mean 1.30 (SD 0.13)) and that TBS had similar discriminative ability to BMD of the femoral neck in detecting vertebral fractures. The literature is promising with respect to the role that TBS can play in predicting VF in axSpA patients; however, clinical application is limited at present due to difficulties with accessing TBS in daily clinical practice.

3.10 EULAR guidelines

In 2015, the European league against rheumatism (EULAR) published guidelines regarding imaging in axSpA (Mandl et al., 2015), which acknowledge the influence of radiographic change on evaluating BMD. This led to the recommendation that hip and PA DXA be used in individuals without syndesmophytes on conventional radiography. In individuals with syndesmophytes, the suggestion is that hip DXA should be used, supplemented by either lateral DXA or qCT. They also recommend that further research needs to be performed to determine which form of imaging provides the best clinical utility for the diagnosis and monitoring of low BMD in axSpA individuals.

These guidelines certainly highlight the issue of low BMD in axSpA individuals, a critically important step, considering only 32% of rheumatologists indicated that assessing for osteoporosis was part of their routine management of AS individuals (Bessant et al., 2003). These guidelines are limited by the lack of evidence available. BMD loss tends to be a progressive process, particularly if untreated, and thus requires serial monitoring. ISCD guidelines state that the same machine should be used to monitor individuals for BMD loss to allow for accurate comparisons (Schousboe et al., 2013). However, inherent to axSpA is the progression of structural damage (Ramiro et al., 2014). Therefore, if EULAR guidelines are strictly followed, PA DXA will be used in early disease, whereas lateral DXA or qCT will be used in later disease, which won't allow accurate comparison of BMD. Clearly, having a guideline which recommends one method of BMD assessment in the early stages of the disease and a different in the later more structurally advanced stages is less than ideal.

3.11 Biomarkers

A biomarker is a biological observation that can predict a clinically relevant endpoint, which is easier and often less expensive to perform than the final measurement (Aronson and Ferner, 2017). They can have multiple roles, including in screening and as prognostic indicators. In axSpA, HLA-B27 is a biomarker for diagnosis, and C-reactive protein and erythrocyte sedimentation rate are biomarkers for disease activity (Reveille, 2015).

3.11.1 Bone turnover markers

Much research has been performed looking at the role of bone turnover markers (BTMs) as biomarkers for osteoporosis in the general population. High levels of BTMs have been shown to predict future fragility fractures in the general population (Greenblatt et al., 2017, Johansson et

al., 2014, Tian et al., 2019), despite not being shown to have a clinically useful role in predicting future bone loss in postmenopausal women (Greenblatt et al., 2017). BTMs also have a role in monitoring response to treatment (Morris et al., 2017).

The literature base examining BTMs in axSpA populations is much smaller than in the general population and the results are conflicting across studies, with no clear relationships demonstrated. In addition, much of the research has focused on identifying individuals at risk of radiographic progression, rather than identifying individuals at risk of osteoporosis. The majority of studies have found no correlation between bone formation markers and BMD (Coiffier et al., 2013, Muntean et al., 2011, Mitra et al., 1999a, Marhoffer et al., 1995, Toussirot et al., 1999, Yilmaz and Ozaslan, 2000); however, Arends et al demonstrated that higher bone formation markers were independently associated with low BMD (Arends et al., 2011). There is a stronger relationship between bone resorption markers and BMD (Coiffier et al., 2013), with a large number of studies finding relationships between higher bone resorption markers and low BMD at the hip (Park et al., 2008, Vosse et al., 2008, Yilmaz and Ozaslan, 2000, Arends et al., 2014, Zhang et al., 2015); however there is very little evidence to support a link between increased bone resorption and lower BMD at the lumbar spine (Yilmaz and Ozaslan, 2000, Coiffier et al., 2013). To our knowledge, all the studies to date investigating the link between BTMs and BMD have used PA DXA when assessing BMD of the spine. Considering the limited ability of PA DXA to detect osteoporosis, it is possible that the studies to date have simply missed significant relationships due to inadequate imaging modalities.

BTMs have also been used in an attempt to understand the pathophysiology of osteoproliferation. Osteocalcin has been shown to be associated with radiographic progression (Gamez-Nava et al., 2016, Pedersen et al., 2011), but the literature base supporting this relationship remains relatively small. The role of bone resorption in osteoproliferation has not been fully elucidated: studies have found no significant association between markers of bone resorption and syndesmophytes (Park et al., 2008, Pedersen et al., 2011), association between CTX-I and mSASSS but not with the presence of syndesmophytes (Gamez-Nava et al., 2016) and associations between higher levels of CTX and osteoproliferation (Arends et al., 2014).

As outlined in Section 3.6.3, there is some evidence that more severe disease in axSpA is associated with osteoporosis. Therefore, using biomarkers to predict individuals with more severe disease may be helpful in identifying individuals at risk of osteoporosis. A systematic review (Coiffier et al., 2013) highlighted a correlation between high BTMs (resorption and formation) and markers of disease activity, including BASDAI, CRP and ESR. However, this link remains

tenuous, with other researchers demonstrating no relationship between BTMs and BASDAI (Gamez-Nava et al., 2016).

3.11.2 Vitamin D

Two separate systematic reviews (Cai et al., 2015, Zhao et al., 2014) found that AS is associated with lower vitamin D concentrations, and that low vitamin D levels appear to be associated with higher disease activity. Vitamin D deficiency has also been associated with functional impairment (Zhao et al., 2017), although not universally (Gula et al., 2018, Zagar et al., 2019). Obermayer et al (Obermayer-Pietsch et al., 2003) detailed an association between the vitamin D receptor, BMD, inflammatory activity and bone metabolism, suggesting a role for vitamin D in the regulation of the immune system. However, several studies have shown no direct relationship between vitamin D levels and low BMD (Mermerci Baskan et al., 2010, Arends et al., 2011, Klingberg et al., 2016). Lange et al used QCT of the lumbar spine to demonstrate lower vitamin D levels in those with osteoporosis (Lange et al., 2005b). Relationships between vitamin D and bone resorption have been demonstrated, which may indicate that vitamin D plays a role in the pathogenesis of osteoporosis through increasing bone turnover (Arends et al., 2011). Therefore, it is conceivable that vitamin D does play an indirect role in osteoporosis in axSpA, through a modulatory effect on the immune system, increasing disease activity and thus leading to osteoporosis. Further research is needed to fully elucidate the link between vitamin D, bone turnover and disease activity, and its impact on BMD.

3.11.3 Testosterone

Testosterone is known to decrease in men with age. Testosterone has a role in maintaining bone mass, and testosterone insufficiency has been associated with bone loss in the general population (Ongphiphadhanakul et al., 1995, Cauley et al., 2010, Saad et al., 2017, Shin et al., 2016). There is controversy regarding the benefit of replacing testosterone to improve bone density (Isidori et al., 2005, Junjie et al., 2019), but it likely has a role in increasing BMD in men with low pre-treatment testosterone levels (Saad et al., 2017). Mitra et al examined the relationship between testosterone and BMD in individuals with mild AS and found no significant correlation (Mitra et al., 1999b). In contrast, Franck et al found that men with osteoporosis in AS had significantly lower levels of testosterone (Franck et al., 2004). However, the literature base investigating this remains small; in particular the ability of testosterone to predict individuals with osteoporosis is unknown.

3.11.4 Serum urate (SUA)

Osteoporosis is a condition characterised by high oxidative stress levels (Sendur et al., 2009, Yang et al., 2014). Oxidative stress has been shown to down-regulate osteoblastogenesis, and thus bone formation (Almeida et al., 2007). Uric acid has antioxidant properties (Ames et al., 1981, Kellogg and Fridovich, 1977), therefore may have a role to play in protecting against osteoporosis. This was examined in the general population with a systematic review and meta-analysis, which showed that hyperuricaemia is independently associated with high BMD and a reduction in fractures (Veronese et al., 2016). Kang et al demonstrated that lower serum uric acid (SUA) levels are associated with lower BMD in AS individuals; however, only males under the age of 50 years were studied (Kang et al., 2015). To our knowledge, no research has been performed looking at the link between SUA and BMD or SUA and fractures in an axSpA cohort.

3.12 Future research areas

Although research into bone loss in axSpA is increasing, with a number of promising avenues, there remains many unknowns. The inherent paradox of osteoproliferation and osteoporosis in axSpA continues to hinder clinicians when accurately assessing and managing the bone loss that occurs in this population. It is largely undisputed that low BMD occurs in axSpA, but more work is needed. The most pressing limitation is the lack of a standardised and accurate method to detect low BMD in this population. Without this, it will remain difficult to accurately define the extent of the problem, as well as determine predictive factors, consequences and the effect of treatment on BMD in axSpA. Lateral DXA is a promising tool. However, the benefit of incorporating lateral DXA into the bone health assessment of individuals with axSpA is unknown, prohibiting its use in clinical practice thus far. Once accurate BMD assessment is a reality, reliable epidemiological data can be collected. Risk factors for low BMD can then be identified, allowing clinicians to predict individuals who are most likely to develop osteoporosis in the future. As part of this, identifying biomarkers which can stratify individuals according to their future risk would be a clinically beneficial tool.

The relationship between osteoporosis and vertebral fractures in axSpA needs to be definitively established, as the relationship is conflicted across studies. An accurate method of measuring BMD of the spine, which is not confounded by osteoproliferation, will allow this relationship to be further explored.

3.13 Conclusion

Osteoporosis is a reality in axSpA. There is a lack of consensus across studies regarding the epidemiology of osteoporosis in axSpA. Accurately assessing BMD is challenging in axSpA due to osteoproliferation. Lateral DXA is a promising tool to overcome this. There is a need for well-designed studies to investigate accurate BMD assessment techniques and osteoporosis epidemiology in this population.

Chapter 4 Measuring Bone Density in Axial Spondyloarthropathy: Time to Turn Things on Their Side?

Material from this chapter has been disseminated in the following publication:

Fitzgerald G, Anachebe T, McCarroll K, O' Shea F. (2020) Measuring bone density in axial SpA: time to turn things on their side? *International Journal of Rheumatic Diseases*. Jan 7. doi: 10.1111/1756-185X.13765. [Epub ahead of print].

(full manuscript in Appendix A).

4.1 Background

Chapter 3 identified the lack of an accurate tool to assess BMD of the spine in individuals with axSpA, which underpins much of the current uncertainty regarding osteoporosis in axSpA. Despite this, it is clear that osteoporosis is prevalent in axSpA, although reported prevalence figures vary widely (Table 3-1 of the narrative review; Chapter 3). Only a small percentage of adults with axSpA in Ireland had an objective assessment of their BMD (Chapter 2); however, 23% of those had osteoporosis. It is possible that selection bias caused this figure to be over-estimated; however, it is equally likely that significant osteoporosis of the spine was missed due to inadequate imaging techniques (Mandl et al., 2015).

Chapter 3 also reported that vertebral fracture prevalence is increased in patients with axSpA (Vosse et al., 2009, Robinson et al., 2013, Montala et al., 2011), with mortality and the potential for devastating neurological outcomes higher than the general population (Westerveld et al., 2009, Westerveld et al., 2014). The reason for the excess vertebral fracture risk is unclear, as the relationship between osteoporosis and vertebral fractures is not as clearly defined as in the general population (Geusens et al., 2015, Klingberg et al., 2012b, Ulu et al., 2013, Donnelly et al., 1994). The risk factors for low BMD are also less well studied in the axSpA population (Ramirez et al., 2018), and there is limited data available to recommend treatment strategies to maintain or improve BMD (Braun et al., 2011, van der Heijde et al., 2017). This is in contrast to strategies that are well delineated in the general population (Black and Rosen, 2016).

Much of the difficulty with estimating BMD of the spine in axSpA is related to the inherent paradox of osteoporosis and osteoproliferation in axSpA; a process which remains incompletely understood (Chapter 3). Conventional dual-energy x-ray absorptiometry (DXA) of the lumbar spine assesses BMD in a posterior-anterior (PA) direction (Schousboe et al., 2013). In axSpA, conventional DXA is unable to distinguish between the BMD of the vertebral body and the BMD of the new osteoproliferation. BMD of the spine can thus be over-estimated when conventional DXA is used, producing an illusion of reassuringly normal BMD, when significant bone loss may have occurred (Carter and Lories, 2011).

A technique where assessment of the spine is unaffected by osteoproliferation is needed to better understand the epidemiology, and ultimately consequences, of low BMD in axSpA patients. Lateral DXA scanning examines the vertebral body from the side, almost exclusively measuring trabecular bone and avoiding much of the osteoproliferation that interferes with BMD assessment of the spine when using conventional DXA (Finkelstein et al., 1994). Modern DXA scanners allow lateral scans to be performed in the supine position and have similar precision to PA scans (Blake et al., 1994). Lateral DXA of the spine in axSpA has been shown in a small number of studies to detect more cases of low BMD than conventional DXA (Malochet-Guinamand et al., 2017, Deminger et al., 2017, Ulu et al., 2013). The International Society of Clinical Densitometry (ISCD) recommend that a diagnosis of osteoporosis is made if the T-score of the lumbar spine, total hip or femoral neck is -2.5 or less (Schousboe et al., 2013). Previous studies investigating the use of lateral DXA in axSpA have been limited by lack of reference databases, prohibiting calculation of T-scores. Therefore, the utility of incorporating lateral DXA in the bone health assessment of individuals with axSpA is unknown.

4.2 Aims

The primary aim of this study was to compare lateral and conventional projections of DXA in their ability to examine BMD of the spine in adults with axSpA. Secondary aims were to (1) assess the prevalence of osteoporosis and vertebral fractures and (2) explore the prevalence of established risk factors for low BMD in this cohort.

The specific objectives of this study were to:

1. compare lateral and PA DXA in their assessment of BMD of the spine in adults with axSpA
2. determine variables (patient and disease-related) that affect the accuracy of conventional DXA

3. assess if including lateral DXA in bone health assessment affects the prevalence of osteoporosis
4. explore associations with low BMD when lateral DXA is included in BMD assessment
5. explore relationships between BMD and vertebral fractures.

4.3 Methods

4.3.1 Study design & setting

This was an observational, cross-sectional, twin-centre study, which took place between April 2017 and January 2018. Recruitment took place between April and November 2017 and the data collection period lasted from May 2017 to January 2018. The study was approved by the joint Tallaght University Hospital/St. James's Hospital Research Ethics Committee, in Dublin. The 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) guidelines for observational studies were followed for the reporting of this study (von Elm et al., 2007).

4.3.2 Population

A convenience sample of participants were consecutively recruited from dedicated spondylitis and general rheumatology clinics in St. James's Hospital and Tallaght University Hospital, Dublin, Ireland. Additionally, patients were identified from the axSpA database and contacted over telephone using a script to invite participation. Participants were eligible if they were adults ($\geq$ 18 years of age) and fulfilled the ASAS criteria for axSpA (Rudwaleit et al., 2009b). Patients were excluded if they were pregnant, actively trying to conceive, breast-feeding, under 18 or had a history of cognitive impairment which precluded informed consent. All data collection was performed in St. James's Hospital, Dublin. Written informed consent was obtained from each participating subject.

4.3.3 Demographic and disease-related data

Data collection included the following:

- Demographics: gender, age, ethnicity, smoking status (never, past, current), alcohol consumption, including units per week, employment status, post-menopausal status for women.

- Disease characteristics: symptom duration, age at diagnosis, extra-articular manifestations (uveitis, inflammatory bowel disease, psoriasis), SpA features (enthesitis, dactylitis, peripheral arthritis), physician-diagnosed history of co-morbidities (ischaemic heart disease, cerebrovascular disease, hypertension, hypercholesterolaemia, diabetes (type 1 or 2), peptic ulcer disease, depression, COPD), axSpA treatment history (biologics, conventional synthetic DMARDs, NSAIDs),
- Osteoporosis history: prior physician-diagnosed osteoporosis (yes/no), prior DXA assessment (yes/no), treatment history (calcium and vitamin D supplements, definitive osteoporosis treatment), osteoporosis risk factors (history of parental hip fracture, early menopause, history of steroid use for greater than 3 months, daily alcohol, type 1 diabetes mellitus, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism, malabsorption, chronic liver disease, eating disorder, history of transplant, hyperparathyroidism, end-stage kidney disease), fracture history (any lifetime fracture, fragility fracture).
- Physical examination: tragus-to-wall, cervical rotation, modified Schober's test, lateral flexion, intermalleolar distance, chest expansion – performed according to a standardised technique (Jenkinson et al., 1994). Height was measured to the nearest 0.1 cm, weight in kilograms (kg). Body mass index (BMI), expressed in kg/m^2, was defined as body weight divided by square of body height.
- Laboratory measurements: routine bloods (full blood count, renal profile, bone profile, liver profile, erythrocyte-sedimentation rate (ESR), C-reactive protein (CRP), parathyroid hormone (PTH), vitamin D), were collected on the same day of assessment and analysed using standard laboratory techniques in St. James's Hospital laboratory. Human leucocyte antigen (HLA) B-27 antigen was reported as positive or negative. Bone turnover markers and testosterone (males only) were also collected for a separate analysis (see Chapter 5).

4.3.4 Outcome measures

The outcome measures used for this study have been previously described (Section 1.9.1).
The following patient-reported outcome measures were collected:

- Bath AS Disease Activity Index (BASDAI) (Garrett et al., 1994)
- Bath AS Functional Index (BASFI) (Calin et al., 1994)
- AS Quality of Life (ASQoL) (Doward et al., 2003)
- Bath AS Patient Global score (BAS-G) (Jones et al., 1996)
- Health Assessment Questionnaire (HAQ) (Pincus et al., 1983).

Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP and ESR were both calculated as described in Section 1.9.1. (Lukas et al., 2009). Bath AS Metrology Index (BASMI) was calculated using the measurements taken by a trained investigator during the physical assessment (Jenkinson et al., 1994). The modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) (Section 1.9.1.7) was calculated from lateral lumbar and cervical spine x-rays, assessing radiographic damage from a scale of 0-72, by two trained readers (Creemers et al., 2005). Antero-posterior pelvic x-rays were performed and read by two trained readers to grade sacroiliitis according to the modified New York criteria (van der Linden et al., 1984).

4.3.5 Bone mineral density

BMD was assessed using a Hologic Horizon A DXA scanner. All BMD assessments were performed by trained radiographers in St. James's Hospital, on the same machine. Lumbar spine BMD was measured in PA (L1-4) and lateral (L2-4, L1 excluded to avoid the overlying 12^{th} rib (Peel et al., 1993)) projections. To obtain the lumbar spine views, participants were supine and straight on the table, with knees supported to adopt a flexed 90 degrees position. The scanner C-arm rotated through 90 degrees to obtain the lateral view of the spine. Participants remained supine for the hip measurements. The scanned leg was extended, abducted 15 degrees and internally rotated through 25 degrees. BMD of the radius (distal third, total, ultradistal) was assessed with the participant seated, side against the table, with the arm resting on the table. Quality control and calibration were performed in accordance with international recommendations (Schousboe et al., 2013). BMD was expressed as g/cm^2. The NHANES III data was used as reference for hip T-scores. The manufacturer's database was used as the reference standard for the lumbar spine T scores, in line with ISCD positions (Shepherd et al., 2015), and T scores were calculated for both PA and lateral spine. Z-scores were not available for lateral spine DXA for male patients.

BMD was categorised according to the World Health Organisation (WHO) for post-menopausal women and men over the age of 50 years as normal if T score >= -1, osteopenia if between -1 and -2.5 and osteoporosis if <=-2.5 (1993). For pre-menopausal women and men under the age of 50 years, a Z score of <-2 was considered to represent low BMD. When calculating prevalence of osteoporosis and osteopenia, only postmenopausal women and men over the age of 50 were included, in accordance with the ISCD positions (Shepherd et al., 2015).

4.3.6 Bias

Selection bias was minimised by using both clinic and database recruitment, to ensure a representative convenience sample. Potential participants were phoned on two separate occasions at different times/days to minimise non-response bias. Volunteer bias was minimised by keeping the data collection time short and offering flexible appointment times.

4.3.7 Statistical methods

Descriptive statistics are presented as frequencies with percentages for categorical variables and mean with standard deviation (SD) for normally distributed data or median with 25^{th} and 75^{th} percentiles for non-normally distributed data. Differences between PA and lateral BMD of the spine were assessed using a two-tailed paired T-test. Relationships between continuous variables were assessed using Pearson's correlation coefficients (r) or Spearman's correlation coefficients (rho) as appropriate. Independent 2-tailed T-tests were used to explore differences in continuous data between two groups and Analysis of Variance (ANOVA) for 3 or more groups. Mann-Whitney U (two groups) or Kruskall-Wallis (three or more groups) tests were used to compare continuous non-parametric variables. Chi-square tests were used to compare categorical variables.

The difference between PA and lateral BMD for each participant was calculated using the formula 'PA BMD minus lateral BMD' and expressed as a new variable in g/cm^2. We developed a model to predict the difference between PA and lateral BMD (dependent variable) from independent variables. Univariable analysis was performed to identify variables associated with the dependent variable and tested in simple linear regression. All variables with a p value of <0.1 in crude analysis were entered in the regression model, along with clinically relevant variables. Normality of residuals and multicollinearity were assessed. IBM SPSS version 24 was used for statistical analysis. A p-value of <0.05 was considered statistically significant.

4.4 Results

4.4.1 Baseline characteristics

A total of 110 participants were recruited between April and November 2017 (see Figure 4-1 for recruitment of participants). Ten participants were unable to undergo DXA assessment of the spine, thus 100 participants with paired PA and lateral DXA of the lumbar spine were included. Participant baseline characteristics are outlined in detail in Table 4-1. Briefly, 78% (n=78) of the studied population were male, 98% (n=98) were Caucasian, mean (SD) age was 51.6 (11.6) years and median (25^{th}, 75^{th}) disease duration was 23.6 (14.4, 34.9) years, with a median delay to diagnosis of 7 (2, 13.5) years. The median (25^{th}, 75^{th}) mSASSS was 10 (IQR 4, 37.3). Eight percent (n=8) of participants had no osteoproliferation on imaging (mSASSS=0) and 8% (n=8) had a 'bamboo spine' (mSASSS=72).

4.4.1.1 Osteoporosis history

Forty percent (n=40) of the cohort had previously had a DXA assessment of their BMD. Seven percent (n=7) of participants report a prior diagnosis of osteoporosis. Although 44% (n=44) of participants reported a history of any fracture in their lifetime, fragility fracture prevalence was low in the cohort (3%, n=3). One third of the cohort (n=33, 33%) had at least one risk factor for osteoporosis: exposure to steroids for greater than three months was the most common risk factor (n=14), followed by a history of parental hip fracture (n=8). Seventeen percent (n=17) of participants were currently taking calcium supplements and 26% (n=26) were taking vitamin D supplements. Five patients had a history of current or past definitive osteoporosis treatment: one patient currently prescribed denosumab and previously prescribed a weekly bisphosphonate, one patient currently and two patients previously prescribed a weekly bisphosphonate, one patient previously treated with intravenous etidronate and one patient previously prescribed strontium ranelate.

4.4.2 Measured BMD of spine (PA and lateral projections of DXA) and hip

Mean BMD of spine and hip are outlined in Table 4-1. All measured sites of BMD correlated positively with each other. BMD of the spine measured by PA (conventional) projection correlated positively with age, mSASSS and BASMI, indicating that PA BMD of the spine increased in older patients and patients with higher mSASSS and BASMI scores (Table 4-2). In contrast, BMD of the spine measured by lateral projection showed no correlation with mSASSS or BASMI, and a non-significant inverse correlation with age; similar patterns were found at the hip. Men had higher BMD than women at the spine (both projections) and the hip. Smoking

status, exposure to biologic treatment, HLA-B27 positivity or presence of osteoporosis risk factors had no impact on BMD (Table 4-3).

4.4.3 Comparison of lumbar spine BMD using PA and lateral DXA

BMD of the lumbar spine measured by PA projection is significantly higher than when BMD is measured by lateral projection (mean difference 0.34 g/cm^2, 95% CI 0.30 to 0.37), as demonstrated in Figure 4-2. The difference between PA and lateral measurements of lumbar spine BMD (PA minus lateral BMD) correlated with age, disease duration, mSASSS, BASMI, BMI and BASFI (see Table 4-2). This indicates that the older the patient or the more severe the disease, the bigger the difference between the PA (conventional) and the lateral BMD measurement. The difference between PA and lateral BMD of the spine was similar in men and women (mean difference between genders was 0.04 g/cm^2, 95% CI -0.04 to 0.12). Additionally, there was no correlation between PA and lateral BMD difference and inflammatory markers or vitamin D ($p>0.05$).

Figure 4-1: Summary of recruitment process of participants. DXA: dual-energy x-ray absorptiometry; PA: posterior-anterior.

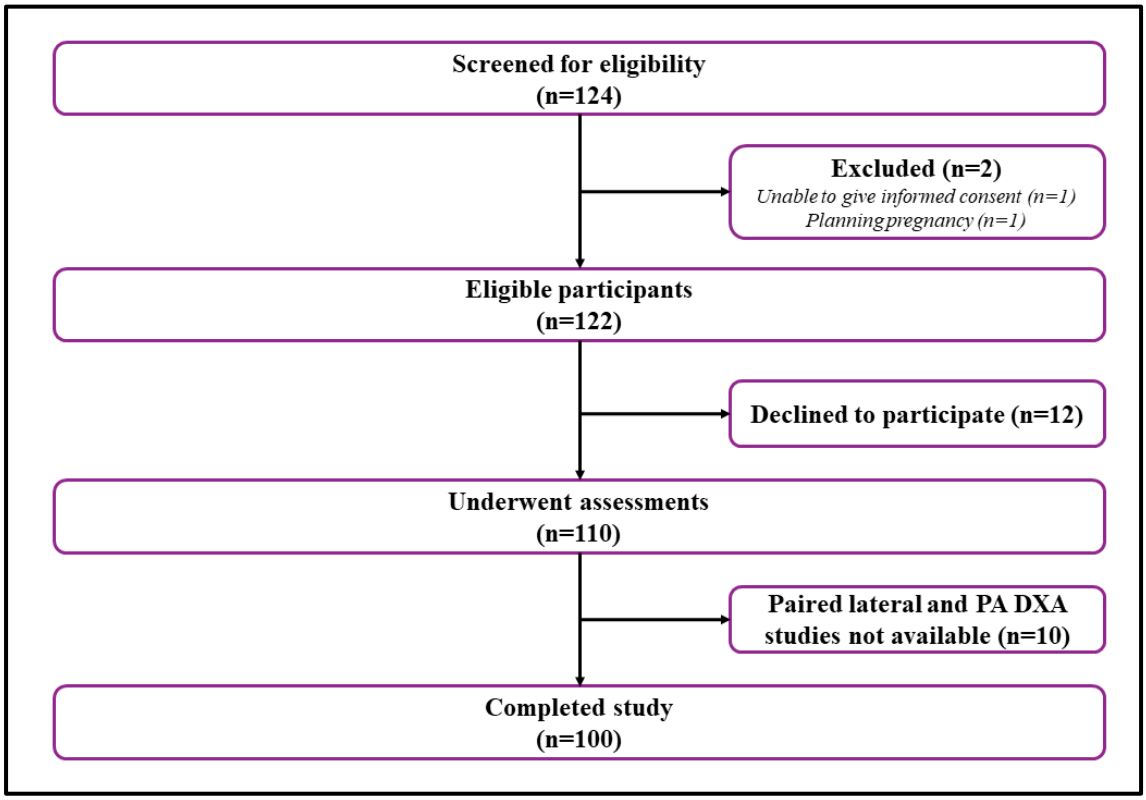


Table 4-1: Baseline demographic and clinical characteristics of the axSpA cohort

Variable	Whole population (n=100)
Males; n (%)	78 (78)
Age, years; mean (SD)	51.6 (11.6)
Caucasian; n (%)	98 (98)
Disease duration, years; mean (SD)	25.7 (12.9)
Delay to diagnosis, years; mean (SD)	8.9 (8.6)
Employment status; n (%)	
Employed	54 (54)
Disability due to axSpA	15 (15)
Smoking status; n (%)	
Current	25 (25)
Past	47 (47)
Never	28 (28)
Postmenopausal women; n (%[§])	13 (59)
HLA-B27 positive*; n (%)	83 (84.7)
BMI, kg/m^2; mean (SD)	28.1 (5.5)
Modified New York criteria; n (%)	85 (85)
Extra-articular manifestations; n (%)	
Uveitis	29 (29)
Psoriasis	16 (16)
IBD	16 (16)
Treatment; n (%)	
NSAIDs	43 (43)
Steroids use >3 months	14 (14)
Biologic exposure	70 (70)
Calcium supplement	17 (17)
Vitamin D supplement	26 (26)
Disease severity; median (25th, 75th percentile)	
ASDAS-CRP	2.2 (1.6, 3.0)
ASDAS-ESR	2.0 (1.3, 2.9)
BASDAI	3.9 (2.1, 5.6)
BASFI	4.0 (1.4, 5.7)
BASMI	4.2 (2.8, 6)
HAQ	0.63 (0.13, 1.00)
ASQoL	6 (2, 11)
mSASSS	10 (4, 37.3)
Bloods, median (25th, 75th percentile)	
Haemoglobin, g/dL	14.6 (13.4, 15.5)
ESR, mm/hr	6 (2, 15)
CRP, mg/L	2.4 (0, 8.1)
Urea, mmol/L	5.0 (4.3, 6.3)
Creatinine, µmol/L	78 (67, 87)
Vitamin D, nmol/L	65 (43, 84)
PTH, pg/mL	40.6 (31.4, 52.3)
Self-reported fragility fracture; n (%)	3 (3)
Osteoporosis risk factor, any; n (%)	33 (33)
Bone mineral density, g/cm^2; mean (SD)	
PA lumbar spine	1.08 (0.19)
Lateral lumbar spine	0.74 (0.14)
Femoral neck	0.80 (0.11)
Total hip	0.96 (0.12)

**HLA-B27 status unknown in n=2. [§]Calculated as % of women (n=22) in study. ASQoL: Ankylosing Spondylitis Quality of Life; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath AS Disease Activity Index; BASFI; Bath AS Functional Index; BASMI: Bath AS Metrology Index; BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HAQ: Health assessment questionnaire; HLA: Human leucocyte antigen; IBD: inflammatory bowel disease; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; NSAIDS: non-steroidal anti-inflammatory drugs; PA: postero-anterior; PTH: parathyroid hormone.*

Table 4-2: Correlation between variables and (a) BMD site (b) difference between PA and lateral BMD.

(a)	Lateral spine BMD§	FN BMD§	TH BMD§	Age§	Disease duration§	BMI§	mSASSS†	BASMI§
PA spine BMD	0.55**	0.48**	0.52**	0.23*	0.15	0.43**	0.41**	0.48**
Lateral spine BMD	…	0.43**	0.55**	-0.12	-0.23*	0.21*	0.07	0.02
FN BMD	…	…	0.82**	-0.19	-0.18	0.18	0.00	0.02
TH BMD	…	…	…	-0.15	-0.16	0.34**	-0.03	-0.06
Age	…	…	…	…	0.70**	0.13	0.55**	0.58
Disease duration	…	…	…	…	…	0.10	0.44**	0.40**
BMI	…	…	…	…	…	…	0.28**	0.30**
mSASSS	…	…	…	…	…	…	…	0.77**

(b)	Age§	BASDAI§	BASMI§	mSASSS†	Disease duration§	BASFI§	CRP§	BMI§
PA – lateral BMD	0.38**	0.01	0.54**	0.51**	0.37**	0.32**	0.03	0.32**

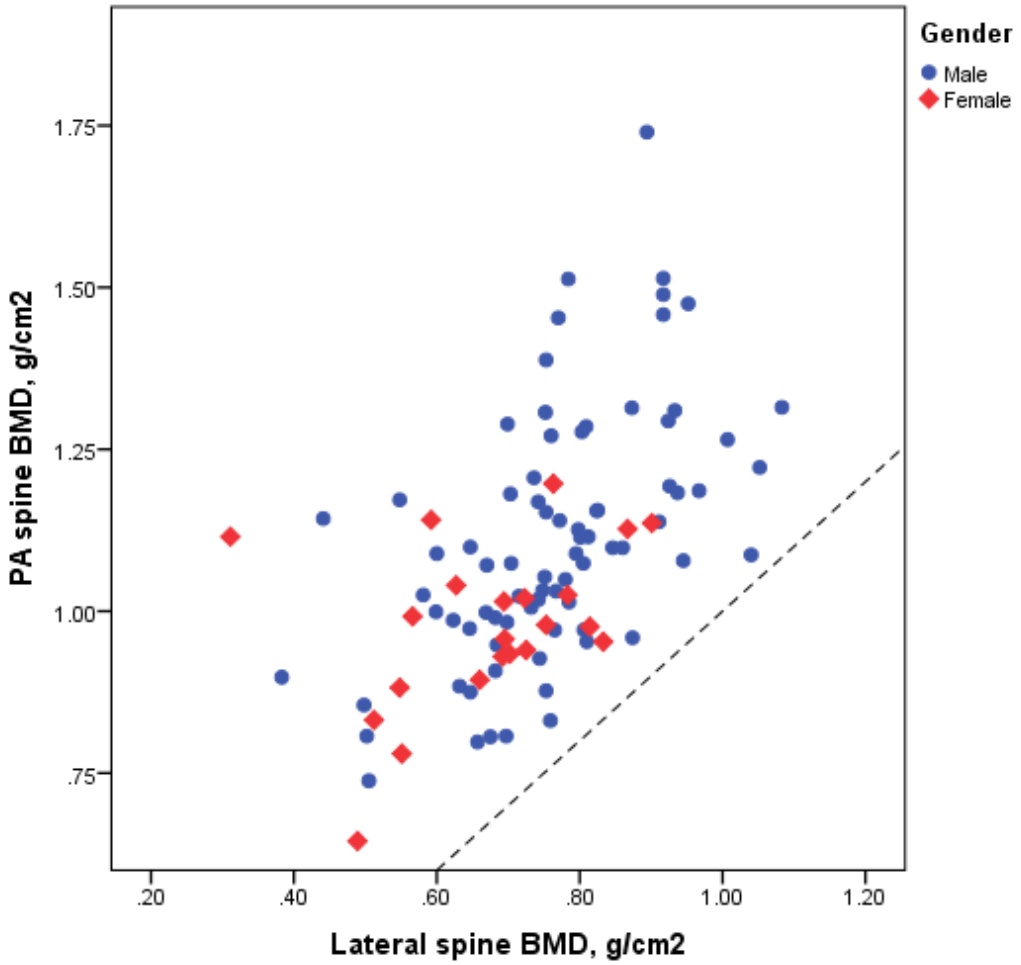
*§ Correlation coefficient is Pearson's r; †Correlation coefficient is Spearman correlation coefficient, rho; ** p<0.01; * p<0.05; … denotes duplicate cell, left blank for clarity of presentation; BASDAI: Bath AS disease activity index; BASFI: Bath AS functional index; BASMI: Bath AS metrology index; BMD: bone mineral density; BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FN: femoral neck; mSASSS: modified Stokes Ankylosing Spondylitis Score; PA: posteroanterior; TH: total hip.*

Table 4-3: Difference in BMD at each measured site for a selection of variables.

Variable	Bone mineral density (BMD), g/cm^2			
	PA spine	Lateral spine	Femoral neck	Total hip
Male	1.11	0.76	0.81	0.98
Female	0.98	0.67	0.75	0.90
P value	***<0.001***	***0.01***	***0.01***	***0.01***
Smoker	1.07	0.74	0.11	0.12
Non-smoker	1.11	0.74	0.11	0.11
P value	*0.40*	*0.97*	*0.71*	*0.99*
Biologic exposure	1.08	0.74	0.80	0.96
No biologic exposure	1.09	0.76	0.79	0.96
P value	*0.74*	*0.52*	*0.77*	*0.98*
HLA-B27 positive	1.08	0.74	0.80	0.96
HLA-B27 negative	1.10	0.76	0.81	0.98
P value	*0.72*	*0.66*	*0.63*	*0.54*
Osteoporosis risk factor*	1.11	0.75	0.78	0.94
No osteoporosis risk factor	1.07	0.74	0.81	0.97
P value	*0.36*	*0.63*	*0.17*	*0.32*

**At least one of: parental hip fracture, steroid use > 3 months, daily alcohol > 2 units, type 1 diabetes mellitus, osteogenesis imperfecta, uncontrolled hyperthyroidism, early menopause, hypogonadism, malabsorption, chronic liver disease, eating disorder, Cushing's disease, transplant, hyperparathyroidism, end-stage kidney disease. HLA: human leucocyte antigen.*

Figure 4-2: Scatter plot demonstrating difference between BMD of the spine as measured by PA and lateral DXA, stratified by gender. Dashed line represents reference for no difference between PA and lateral BMD. DXA: dual-energy x-ray absorptiometry; PA: posterior-anterior.



4.4.4 Prediction of difference between PA and lateral BMD

We developed a model to predict the difference between PA and lateral BMD, as outlined in the methods section. As well as variables with a p-value of <0.01 in crude analysis, we additionally controlled for gender and exposure to treatment with biologics as clinically relevant variables. Age and disease duration were strongly correlated, therefore only disease duration was included in the final model. After correcting for multicollinearity, the R^2 of the final model was 0.4 (Table 4-4). Disease duration, BMI and mSASSS remained independent predictors of the difference between PA and lateral BMD of the spine.

Table 4-4: Multiple regression model, variables associated with difference between PA and lateral BMD of the spine. BMD: bone mineral density; PA: posterior-anterior.

Variable	ß	95% CI	P Value
Gender[a]	-0.028	-0.093 to 0.037	0.40
Disease duration	0.003	0.001 to 0.005	**0.01**
Biologic exposure[b]	0.015	-0.043 to 0.072	0.60
BMI	0.009	0.003 to 0.014	**<0.01**
mSASSS	0.002	0.001 to 0.004	**<0.01**

a: reference group (0) is male; b: reference group (0) is no biologic exposure; BMI: body mass index; CI: confidence interval; mSASSS: modified Stokes Ankylosing Spondylitis Spinal Score.

4.4.5 Prevalence of low BMD according to WHO criteria

Fifty-seven patients fulfilled criteria for classification of low BMD using T scores (i.e. men ≥ 50 years and post-menopausal women). Of this cohort, 16% had low BMD of the spine when measured by PA DXA, compared to 47% when measured by lateral DXA (chi-square 7.4, p=0.01, OR 12.2, 95% CI 1.4 to 106), as demonstrated in Figure 4-3. At the hip, 34% (n=19) had low BMD at either femoral neck or total hip.

As per the WHO definition (1993), whereby a diagnosis of osteoporosis is made if a person fulfils criteria at hip OR spine, hip and spine data was combined to assess for low BMD at any site. When PA spine BMD was combined with hip BMD, 35% (n=20) of participants had low BMD at a minimum of one site. However, when lateral spine BMD was combined with hip BMD, 56%

(n=32) of participants had low BMD, a statistically significant difference (Chi-square 18.9, df 1, p<0.001).

Including both PA and lateral spine in combination with hip data, 58% (n=33) of the cohort had low BMD and 18% (n=10) had osteoporosis at a minimum of one site.

Z scores for lateral lumbar spine BMD were not available in men, therefore similar data cannot be presented for the remainder of the population.

4.4.5.1 Localised versus systemic osteoporosis

BMD of the distal third of the radius correlated with BMD at the PA spine (r=0.27, p=0.01), lateral spine (r=0.33, p=0.001), femoral neck (r=0.39, p<0.01) and total hip (r=0.37, p<0.01). Four participants (n=7%) had low BMD at the distal third of the forearm, according to the WHO criteria. This was significantly less than the prevalence of low BMD at the lateral spine (χ^2=4.8, p=0.03), and a trend towards a lower prevalence than at the hip (χ^2=3.2, p=0.07).

4.4.6 Associations with low BMD

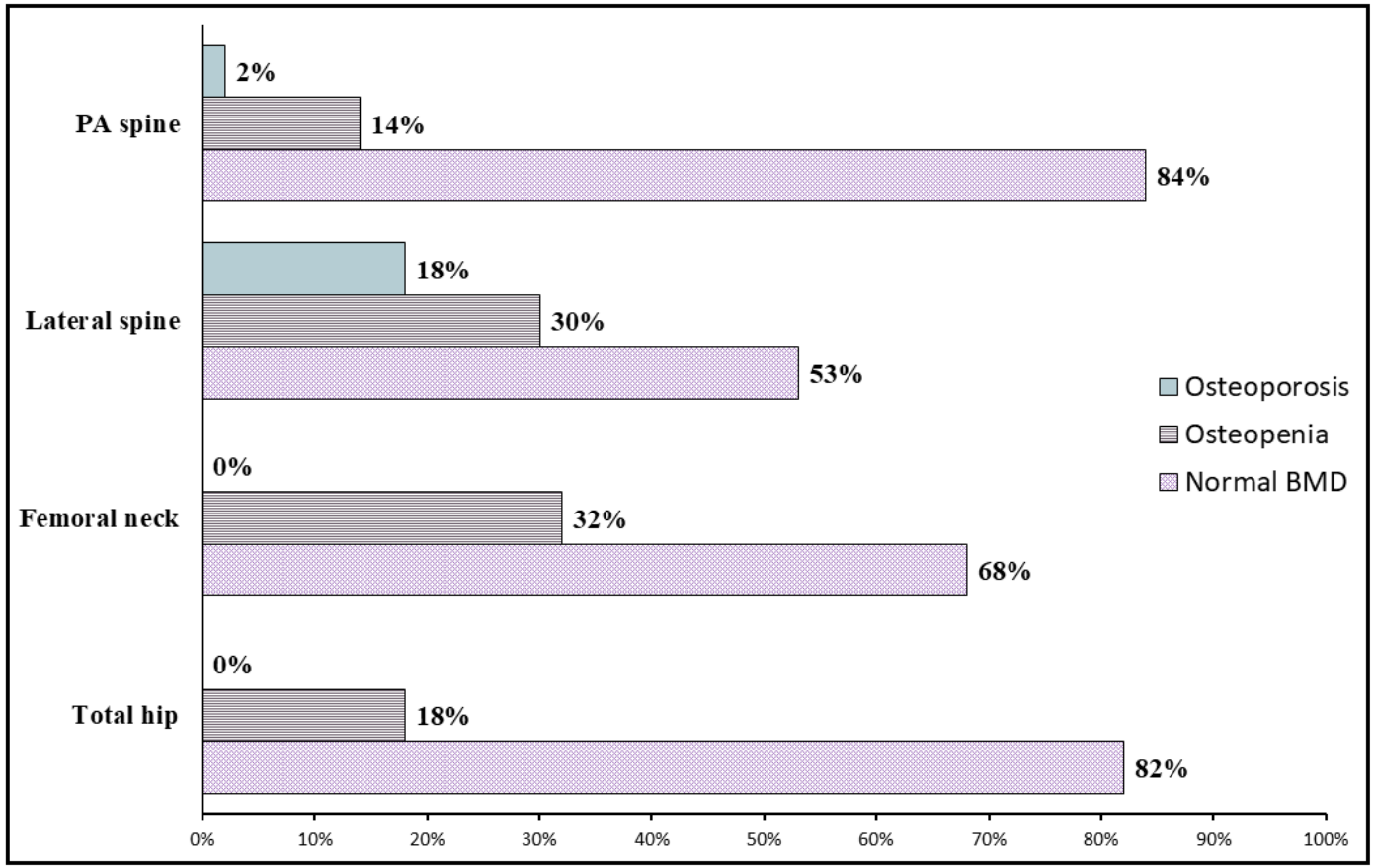
4.4.6.1 Demographic and baseline clinical characteristics

More women than men had low BMD (85% v 50%, χ^2=4.9, p=0.03). There was no difference in age or length of disease between patients with and without low BMD. Significantly more patients with low BMD were HLA-B27 positive than those with normal BMD (88% v 65%, χ^2=4.13, p=0.04). There was a greater proportion of participants with at least one osteoporotic risk factor and low BMD (75%) compared to those with low BMD and no traditional risk factors (49%); however, this difference did not reach statistical significance (χ^2=3.7, p=0.05). BMI was lower in patients with low BMD than those with normal BMD (27.3 v 29.7), but this was not statistically different (MD 2.4, 95% CI -0.2 to 5.0, p=0.07). Smoking status had no effect on BMD.

4.4.6.2 AxSpA-related characteristics

Biologic and NSAID use had no effect on the prevalence of low BMD. There was no significant difference in any disease outcome measures between participants with normal or low BMD. CRP and ESR were both higher in participants with low BMD than those with normal BMD, but this did not reach statistical significance (8.4 v 5.1, p=0.21, and 15.8 v 12.5, p=0.59 respectively). The presence or absence of EAMs did not change the frequency of low BMD.

Figure 4-3: Prevalence of normal bone mineral density, osteopenia and osteoporosis at each measured site, in men ≥ 50 years and post-menopausal women (n=57). Reported figures are percentage; BMD: bone mineral density; PA: posterior-anterior.



4.4.7 Associations with osteoporosis

4.4.7.1 Demographic and baseline clinical characteristics

A higher proportion of women than men had osteoporosis (46% v 9%, χ^2=9.5, p=0.002). There was a higher prevalence of osteoporosis in participants with hypertension than without (31% v 7%, χ^2=5.8, p=0.02). Participants with osteoporosis had significantly longer disease duration than those without osteoporosis (39 v 30 years, p=0.03), yet age profile was similar between the two groups (62 v 60 years, p=0.34). However, participants with osteoporosis had an age of diagnosis seven years younger than those without, although this did not reach statistical significance (95% CI -0.4 to 14.8, p=0.06).

4.4.7.2 AxSpA-related characteristics

There was no difference in any disease outcome measures between those participants with and without osteoporosis. There was no significant pattern noted in the usage of biologics or NSAIDs amongst participants with osteoporosis.

4.4.8 Fractures

Three participants reported a previous fracture which fulfilled the criteria for a fragility fracture. Three additional vertebral fractures were detected on the VFA, therefore in total, there were six fragility fractures in the cohort. All six participants were male and HLA-B27 positive. They had a mean (SD) age of 56 (12) years, with a mean disease duration of 31 (13) years: although these were higher than the participants without fractures (51 (12) and 25 (13) years respectively), this was not statistically significant. No participants with a fracture were taking calcium or vitamin D supplements, or had ever been prescribed definitive osteoporotic treatment.

Of the six fragility fractures, four were vertebral fractures. Participants with a vertebral fracture had significantly higher BMD of the spine when measured by PA DXA (1.38 v 1.07, MD 0.32, 95% CI 0.13 to 0.50), but not by lateral DXA (0.81 v 0.74, MD 0.06, 95% CI -0.08 to 0.21). There was no difference in BMD at the hip. MSASSS was higher in participants with vertebral fractures than those without (45 v 22), but this difference did not reach statistical significance (95% CI -2 to 48). There was no difference in any other disease outcome measures between participants with and without VF.

4.5 Discussion

Osteoporosis is widely accepted to occur at an increased prevalence in axSpA compared to age- and sex-matched controls. However, accurately assessing BMD of the spine is challenging in axSpA patients due to overestimation that occurs from calcification and osteoproliferation (Fitzgerald and O'Shea, 2017). Therefore, the primary aim of this study was to compare PA and lateral DXA in their ability to measure BMD of the spine and assess the impact of osteoproliferation.

In this study of 100 axSpA patients, we demonstrated that when directly compared, raw BMD of the spine expressed in g/cm^2 was significantly lower when measured by lateral projection of DXA than by conventional PA DXA, confirming findings by other researchers (Klingberg et al., 2012c, Malochet-Guinamand et al., 2017). We then explored the association of a number of participants and disease-related variables with PA and lateral DXA, in an attempt to explain the difference between the two methods. We demonstrated that PA BMD of the spine increased with age, in contrast to the expected decline in BMD that occurs with age in the general population. PA BMD also increased as mSASSS and BASMI increased, both indicators of structural severity. These associations were not seen when BMD of the spine was measured by lateral DXA, or with hip BMD. Therefore, longer disease duration and more severe disease affected PA DXA assessment of the spine, but not lateral DXA.

We also demonstrated that the difference in BMD between PA and lateral DXA increased with longer disease duration and higher mSASSS. After controlling for BMI due to its effect on measurement of BMD from soft-tissue interference (Rajamanohara et al., 2011, Patel et al., 2000), mSASSS and disease duration remained independent predictors of the difference between PA and lateral DXA of the spine. This confirms previous research (Klingberg et al., 2012c) which also demonstrated that the difference between PA and lateral BMD of the spine correlated with mSASSS. This important finding signifies that structural damage in the form of osteoproliferation is interfering with the accuracy of what is currently our 'gold standard' technique to assess BMD in axSpA patients (Schousboe et al., 2013). Therefore, continuing to rely solely on PA DXA to evaluate BMD of the spine in axSpA is no longer acceptable.

The clinical significance of BMD is not in the raw BMD expressed in g/cm^2, but in its WHO classification as normal or low BMD using T scores, as it is this which is clearly associated with morbidity and mortality in the general population (Kanis, 2002, Qu et al., 2013). Previously, the ability of lateral spine DXA to detect low BMD in axSpA was limited by lack of adequate reference databases in other studies to compute T scores (Deminger et al., 2017, Malochet-

Guinamand et al., 2017). In our study, a manufacturer-compiled reference database allowed us to compute T scores (but unfortunately not Z scores) for both men and women. Therefore, we compared the ability of lateral and PA DXA to measure BMD and found that lateral DXA detected significantly more cases of low BMD (47%) than did PA DXA (16%).

The WHO criteria recommend that a diagnosis be made if a patient fulfils criteria for osteopenia or osteoporosis at either the spine or the hip (1993, 1994). To date, PA DXA has been used for this. In our study, using lateral DXA in place of PA DXA increased our diagnosis of low BMD significantly from 35% to 56%. Using both PA and lateral spine DXA results, along with hip data, increased the diagnosis of low BMD to 58%. Had we relied on hip data alone, as advocated by some clinicians (Deminger et al., 2017), only 34% of patients would have received a diagnosis of low BMD. Thus, using lateral DXA in addition to PA DXA to assess BMD increased our ability to detect low BMD in axSpA. In the general population, lateral DXA has been shown to identify more cases of low BMD than conventional DXA (Zmuda et al., 2000, Finkelstein et al., 1994). To our knowledge, this is the first study in axSpA to demonstrate this.

Risk factors for low BMD in axSpA have been conflicted in the literature, largely due to a small evidence base and limitations in BMD assessment methods (see Chapter 3). Having established that lateral DXA improves the detection of low BMD in this population, the next step was to explore the relationship with established risk factors. Low BMD was considered present if the T score was <-1 and osteoporosis if the T score was ≤-2.5 at either the hip and/or the spine (PA or lateral). The analysis was limited to postmenopausal women and men over the age of 50 years, as applies to the interpretation of T scores. More women than men had both low BMD (85% v 50%) and osteoporosis (46% v 9%), unsurprising considering the female sex is a well-known risk factor for osteoporosis in the general population (Compston et al., 2019); however, the number of women in this subgroup was small (n=13), so caution is needed when interpreting this result.

The finding that HLA-B27 positivity is higher in patients with low BMD than those with normal BMD (66% v 33%) is interesting. Klingberg et al found lower BMD in the radius of HLA-27 negative patients compared to HLA-B27 positive patients, but no difference at other sites (Klingberg et al., 2012c). To our knowledge, this finding of low BMD in HLA-B27 positive patients has not been demonstrated in humans with axSpA. There are a number of mouse studies showing that HLA-B27 transgenic rats have more bone fragility and lose bone density at an increased rate than controls (Akhter and Jung, 2007, Rauner et al., 2009, Rauner et al., 2015). Therefore, this finding needs to be investigated further in humans.

There was no significant association between low BMD or osteoporosis and any axSpA disease outcome measures. The results were also unable to demonstrate any relationship with treatment patterns, either with NSAIDs or biologics, past or present. As many of these outcome measures reflect current disease activity, longitudinal studies will be better placed to identify whether prolonged active disease makes osteoporosis more likely in axSpA. However, these results suggest that the presence of osteoporosis cannot currently be predicted based on disease severity. In light of this, routine screening for individuals with axSpA may be required, independent of the severity of disease.

The prevalence of fragility fractures in this cohort was very low, prohibiting any detailed analysis into relationships between fractures and BMD. This may be as a result of the overall relatively young age of the study population (52 years). However, it is worth noting that PA spine BMD was significantly higher in those with vertebral fractures compared to those without, whereas there was no difference in lateral spine BMD. There was also a suggestion of a higher mSASSS in those with vertebral fractures, but the difference, although clinically large (45 v 22), didn't reach statistical significance. Although the existing literature base is small, previous studies have similarly found that mSASSS is associated with vertebral fractures (Pray et al., 2017). This tentatively suggests that osteoproliferation may play a more important role in vertebral fracture risk than BMD, but much more research is needed with a large controlled cohort of axSpA patients with vertebral fractures. Our prevalence of fragility fractures was too small to reliably rule out an association with low BMD.

It has been the subject of much debate as to whether osteoporosis in axSpA is localised to the spine or is a more systemic process (Karberg et al., 2005, Toussirot et al., 2001, Sarikaya et al., 2007, Klingberg et al., 2012c). We demonstrated a higher prevalence of low BMD at the spine compared to the hip, and much higher than at the radius, suggesting the spine is affected to a more significant degree than are the hips. Therefore, it is important that we have a method to accurately assess BMD of the spine, which isn't affected by the severity of disease. We note the interesting results of a recent study published (Deminger et al., 2017) which was the first to examine lateral measurements of the spine longitudinally and unexpectedly found that both lateral and PA BMD increased over time. However, there were no reference values available for lateral BMD measurements in the men, so the authors urge caution with interpretation of this finding. The ISCD advises that the lateral spine may have a role in monitoring (Shepherd et al., 2015). Therefore, the investigation of the role of lateral DXA in axSpA for evaluating changes in BMD over time should be a priority for future research.

4.5.1 Limitations

This is a cross-sectional study, which prohibits comment on causality – we can merely comment on associations. Also, the population is almost exclusively Caucasian, thus caution must be applied when extrapolating results to other ethnicities. Reference values to calculate Z scores for lateral spine BMD were unavailable, thus the prevalence of low BMD in men under 50 years and pre-menopausal women cannot be commented upon. However, the difference between raw BMD values are valid in the entire population. A convenience sample was chosen for this study, thus the sample may not be representative of the Irish axSpA population. As outlined in section 4.3.6, all efforts were taken to minimise this bias. The participants included in this study were older and had a 10 year longer disease duration than in ASRI, with a higher percentage fulfilling mNY criteria. However, baseline characteristics including gender breakdown, ethnicity and HLA-B27 status were similar, allowing the results of this study to be extrapolated to the wider Irish axSpA population. Finally, the clinical significance of osteoporosis is in its associated fracture risk; however, as acknowledged in the discussion, the prevalence of fragility fractures was low in this study. This prevented any definitive conclusions regarding the association between BMD and vertebral fractures. The clinical outcomes of vertebral fractures in participants with axSpA are worse than other populations (Westerveld et al., 2009), so it is crucial to understand the role BMD plays in this increased susceptibility. Therefore, future research needs to determine whether there is a correlation between BMD as measured by lateral DXA and vertebral fracture risk.

This study has many strengths. The patients are well-characterised, with an extensive data set collected. It is a homogenous population, allowing easy extrapolation of the results. All efforts were made to limit sources of bias, thus ensuring our population is representative of the axSpA population.

4.6 Conclusion

In summary, BMD of the lumbar was significantly lower when measured by lateral DXA than PA DXA. The difference between lateral and PA DXA increased with higher mSASSS. Including lateral DXA in the bone health assessment significantly increased the prevalence of low BMD in this population. Lateral DXA should be routinely added to the BMD assessment of individuals with axSpA.

Chapter 5 Biomarkers in axSpA: bone turnover markers, serum urate, vitamin D, testosterone

5.1 Introduction

Assessing BMD of the spine accurately in axSpA is challenging (see Chapter 3). Adding lateral DXA to the BMD assessment of individuals with axSpA, as a technique which is largely unaffected by osteoproliferation, permits a more comprehensive evaluation of BMD of the spine. Incorporating lateral DXA assessment in a cross-sectional study of 100 adults with axSpA identified a high prevalence of osteopenia and osteoporosis (Chapter 4).

Although lateral DXA allows us to identify more participants with existing osteoporosis, it remains a challenge to identify which participants are at risk of developing osteoporosis in axSpA. The lack of a consensus regarding definite clinical and disease-related predictors has been demonstrated in the literature (Chapter 3) and was confirmed by the cross-sectional study (Chapter 4).

As outlined in Section 3.9.1, biomarkers are biological observations that can predict a clinically relevant endpoint (Aronson and Ferner, 2017). They have a role in axSpA in accurately assessing disease activity, predicting response to treatment and predicting radiographic progression (Danve and O'Dell, 2015). Identifying biomarkers which could predict the development of osteoporosis in axSpA may improve outcomes, considering the knowledge that early intervention in postmenopausal women delays progression and improves outcomes (Compston et al., 2019, Cosman et al., 2014). Potential biomarkers that may be suitable are bone turnover markers (BTMs), vitamin D, testosterone in men and serum urate (SUA), all of which are introduced in Section 3.9.1.

5.2 Aims

The aims of this study were to:

1. Examine the association between biomarkers and bone health in axSpA, with the following objectives:
    a) Investigate the relationships between BMD and a variety of biomarkers, specifically BTMs (CTX-I, P1NP & osteocalcin), vitamin D, testosterone, SUA
    b) Explore relationships between biomarkers and fragility fractures.
2. Assess the relationship between bone loss and osteoproliferation using biomarkers.
3. Investigate the relationship between biomarkers and disease activity in this population.

5.3 Methods

5.3.1 Study design, setting & population

The methods for this study have been outlined in detail in Chapter 4, Section 4.3. This was an observational, cross-sectional, twin-centre study, which took place between April 2017 and January 2018. The population was adults with axSpA according to the ASAS criteria. Participants were recruited as outlined in Section 4.3.2. Additional exclusion criteria were applied for this analysis: participants without BTM samples; participants with a history of current or past treatment with osteoporosis treatment, defined as anti-resorptive medications (bisphosphonates, denosumab), anabolic medications (teriparatide) or strontium ranelate.

5.3.2 Data collection

The data collection methods for this study are outlined in detail in Section 4.3. Blood samples were collected in the morning and following an overnight fast, to avoid the confounding effect of the circadian pattern and food intake on BTMs (Szulc et al., 2017). Blood samples for CTX-I, P1NP and osteocalcin were centrifuged and separated within two hours of collection and stored at -80^{o}C until analysis. BTMs were analysed by the Roche Modular Cobac system using chemiluminescence enzyme immunoassay commercial kits in the laboratory in St. James's Hospital. Reference ranges used for BTMs were appropriate for age, gender and menopausal status. Vitamin D was analysed using liquid chromatography-tandem mass spectrometry (API 4000; AB SCIEX) in the Biochemistry laboratory of St. James's Hospital. The Institute of Medicine vitamin D guidelines were used to categorise vitamin D levels into deficient (<30 nmol/L), insufficient (30-50 nmol/L) and sufficient (>50 nmol/L) (Del Valle et al., 2011). BMD

of the lumbar spine (PA and lateral), hip (femoral neck and total) and radius (distal third, total, ultradistal) was assessed, as outlined in Section 4.3.5.

5.3.3 Statistical analysis

Descriptive statistics are presented as frequencies with percentages and mean with standard deviation (SD) or median with 25th and 75th percentiles, as appropriate, for categorical and continuous variables respectively. Relationships between continuous variables were assessed using Pearson's correlation coefficients (r) for normally distributed variables or Spearman's correlation coefficients (rho) for non-normally distributed variables. Independent 2-tailed T-tests (two groups) or Analysis of Variance (ANOVA; three or more groups) were used to explore differences between groups in continuous data for normally distributed data. Mann-Whitney U-test or Kruskall-Wallis tests were the equivalent non-parametric tests. Chi-square tests were used to compare categorical variables.

The assumption of normality was tested both visually using Q-Q plots and histograms, and statistically using the Shapiro-Wilk normality test ($p<0.05$ indicated breach of normality). If the assumption of normality was violated, a log10 transformation was applied to the variable (CTX, P1NP and osteocalcin were transformed in this manner) to achieve normality.

Univariable and multivariable regression analyses were used as appropriate to test relationships between one or more independent variables and a dependent variable. Normality of residuals and multicollinearity were assessed. All appropriate assumptions were tested and met for each test. A 2-tailed p-value of <0.05 was considered statistically significant. IBM SPSS version 24 was used for statistical analysis.

5.4 Results

5.4.1 Baseline characteristics of the participants

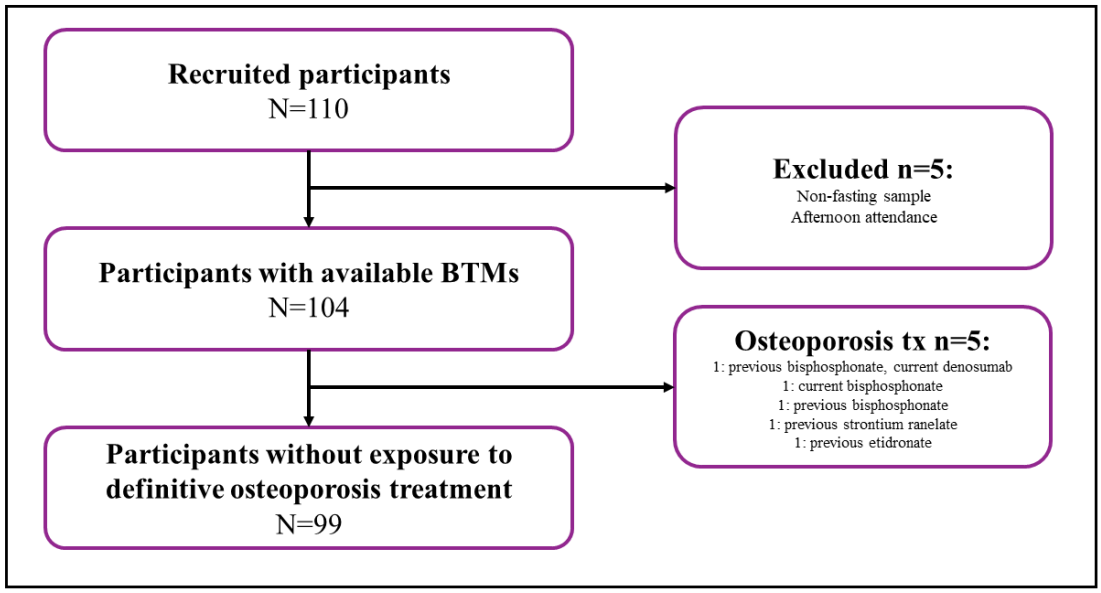
Of the 110 recruited participants, 99 participants were included in analysis of biochemical markers (see Figure 5-1). Table 5-1 outlines the baseline demographic and clinical characteristics of the cohort, of whom 77% (n=76) were male, mean (SD) age was 50.3 (12.4) years and 98% (n=97) were Caucasian. The mean BASDAI (3.9) reflects mild to moderate disease burden. Forty-eight percent (n=47) had a history of a fracture in their lifetime, with six participants fulfilling criteria for a fragility fracture. Four of the fragility fractures were vertebral fractures. Fourteen percent (n=14) of participants had at least one fall in the past twelve months.

Table 5-1: Baseline demographic and clinical characteristics

Variable	Whole population (n=99)
Male; n (%)	76 (77)
Age, years; mean (SD)	50.3 (12.4)
Caucasian; n (%)	97 (98)
Disease duration, years; mean (SD)	24.4 (12.8)
Delay to diagnosis, years; mean (SD)	9.0 (5.6)
Smoking status; n (%)	
Current	25 (25)
Past	44 (44)
Never	30 (30)
Post-menopausal women; n (%)*	12 (52)
HLA-B27 positive; n (%)	89 (86)
BMI, kg/m^2; mean (SD)	28.4 (5.6)
mNY criteria; n (%)	80 (81)
Treatment; n (%)	
Current biologic use	56 (57)
Ever biologic use	68 (69)
Vitamin D levels; n (%)†	
Sufficient (>50)	62 (63)
Insufficient (30-50)	30 (30)
Deficient (<30)	7 (7)
Disease severity; median (25th, 75th percentile)	
BASMI	4.0 (2.7, 5.8)
BASDAI	3.9 (2.6, 5.6)
ASDAS-CRP	2.1 (1.5, 3.0)
ASDAS-ESR	2.0 (1.3, 2.8)
BASFI	3.7 (1.4, 5.6)
ASQoL	6.0 (2.0, 11.0)
HAQ	0.5 (0.0, 0.9)
mSASSS	8.5 (3.0, 33.1)

**23 women; †using Institute of Medicine thresholds (Del Valle et al., 2011). ASDAS: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis Quality of Life Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; HLA: human leucocyte antigen; mNY: modified New York; mSASSS: modified Stoke Ankylosing Spinal Spondylitis Score; n: number; SD: standard deviation.*

Figure 5-1: Flow of participants in biomarkers study.



5.4.2 Bone turnover markers

Descriptive data

BTM values were compared to age, gender and menopausal status-appropriate reference ranges. Median (25^{th}, 75^{th} percentiles) values are presented in Table 5-2. Eight percent of participants had a CTX value above normal and no-one had a low level. Ten percent of participants had a P1NP value above normal and no-one had a low P1NP level. Ten percent had a low osteocalcin level and one patient had a high osteocalcin level. All three BTMs correlated with each other, with the strongest correlation between P1NP and osteocalcin (see Table 5-3). Of the eight participants with a high CTX, 50% (n=4) also had a high P1NP and one participant had a high osteocalcin level. CTX was significantly correlated with increasing age (rho 0.3, p=0.01). BTMs were not significantly correlated with any other baseline characteristics of the cohort, as outlined in Table 5-3. There was no relationship between BTMs and disease or radiological severity. BTM levels did not differ between males and females (Table 5-2), fulfilment of mNY criteria, smoking status, presence of comorbidities, use of NSAIDs or use of biologics, either currently or ever.

Table 5-2: Description of biomarkers (median, 25th, 75th), with comparison between genders.

	Whole group (n=99)	Males (n=76)	Females (n=23)	P value*
CTX, *ng/mL*	0.35 (0.25, 0.48)	0.35 (0.25, 0.46)	0.37 (0.22, 0.54)	0.96
P1NP, *ng/mL*	43.2 (35.8, 57.9)	43.4 (35.7, 57.6)	41.9 (36.0, 65.4)	0.76
Osteocalcin, *ng/mL*	21.6 (16.9, 27.3)	21.7 (16.7, 25.1)	21.5 (17.5, 30.3)	0.96
PTH, *pg/mL*	40.3 (30.7, 50.2)	40.7 (30.9, 52.9)	33.9 (29.6, 45.8)	0.21
Vitamin D, *nmol/L*	62.0 (43.0, 79.0)	63.0 (43.0, 74.8)	57.0 (43.0, 110.0)	0.96

**Mann-Whitney U test. CTX: C-terminal telopeptides of type 1 collagen; P1NP: N-propeptide of type 1 collagen; PTH: parathyroid hormone*

Table 5-3: Correlation between bone turnover markers and baseline characteristics, including bone mineral density, of the cohort.

	CTX *Rho*	Osteocalcin *Rho*	P1NP *Rho*
CTX	**…**	**0.69***	**0.67***
Osteocalcin	**0.69***	…	**0.84***
P1NP	**0.67***	**0.84***	…
PTH	**0.25***	0.15	0.07
Vitamin D	-0.00	0.04	-0.04
Age	**0.26***	-0.02	-0.08
Disease duration	0.19	0.05	-0.01
Delay to diagnosis	0.17	0.13	0.13
BMI	0.03	-0.12	-0.07
PA spine BMD	0.01	-0.03	-0.06
Lateral spine BMD	-0.04	-0.02	-0.05
Femoral neck BMD	-0.20	-0.12	-0.05
Total hip BMD	-0.09	-0.07	-0.03
Distal third forearm BMD	-0.18	-0.18	-0.19
Total forearm BMD	-0.17	-0.18	-0.13
Ultradistal forearm BMD	**-0.24***	**-0.24***	-0.18
mSASSS	0.09	0.06	-0.03
BASDAI	-0.15	-0.20	-0.13
BASMI	0.14	0.05	0.01
ASDAS-ESR	-0.01	0.00	-0.02
ASDAS-CRP	-0.07	-0.12	-0.14

**denotes significance<0.05. ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BMD: bone mineral density; BMI: body mass index; CRP: C-reactive protein; CTX: C-terminal telopeptides of type 1 collagen; ESR: erythrocyte sedimentation rate; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; P1NP: N-propeptide of type 1 collagen; PA: posterior-anterior; PTH: parathyroid hormone.*

BTMs and bone mineral density in the whole cohort

Sixteen percent (n=15) of the cohort had a diagnosis of osteoporosis in at least one measured site. CTX and osteocalcin correlated negatively with BMD measured at the ultradistal forearm (rho -0.24, p=0.02 in both cases). BTMs did not correlate with BMD at any other site in the cohort as a whole (Table 5-3).

When stratified by gender, in women (n=20), CTX correlated negatively with BMD at the PA spine (rho=-0.49, p=0.03), femoral neck (rho=-0.57, p=0.01) and forearm (distal forearm rho -0.53, p=0.02, total forearm rho -0.59, p=0.01, ultradistal forearm rho -0.54, p=0.01). There was no relationship between P1NP or osteocalcin and BMD at any site in women. In men, CTX was negatively correlated only with ultradistal forearm BMD (rho=-0.23, $p<0.05$).

There was no significant difference in CTX, P1NP or osteocalcin levels between those participants with and without osteoporosis. Participants who had a previous fracture had significantly higher P1NP than those without any history of fracture (55.6 versus 45.1, p=0.04).

BTMs in WHO T-score population: men ≥ 50 years and postmenopausal women

There were 51 participants in this subgroup: 77% (n=39) male, 96% (n=49) Caucasian, 10% (n=5) with a history of a fragility fracture, 47% (n=24) currently taking biologics, 78% (n=40) HLA-B27 positive. The mean (SD) age was 60.3 (7.3) years, with a mean disease duration of 31 years (12.6) and delay to diagnosis of 11.5 (10.6) years. Median (25^{th}, 75^{th} percentile) mSASSS was 26 (7.8, 48). The prevalence of normal BMD, osteopenia and osteoporosis in this subgroup are demonstrated in Figure 5-2.

In this population, CTX negatively correlated with BMD of femoral neck (rho -0.37, p=0.01), total hip (rho -0.37, p=0.01) and forearm (distal forearm rho -0.36, p=0.01, total forearm rho -0.38, p=0.01, ultradistal forearm rho -0.41, $p<0.01$). Osteocalcin negatively correlated with BMD of femoral neck (rho -0.33, p=0.02), and distal forearm (rho -0.29, p=0.04). P1NP correlated negatively with BMD of PA lumbar spine (rho -0.29, $p<0.05$), and forearm (distal forearm rho -0.31, p=0.03, total forearm rho -0.31, p=0.03, ultradistal forearm rho -0.32, p=0.02).

Participants with low BMD at the femoral neck had significantly higher CTX and osteocalcin than participants with normal BMD (see Figure 5-3). There was no difference in P1NP levels between participants with low and normal BMD of femoral neck. BTMs did not differ between participants with low and normal BMD at spine (PA or lateral), total hip or distal radius. There was no difference in BTMs between participants with and without a history of fracture (fragility or otherwise) or falls.

Figure 5-2: Breakdown of BMD categories, in men ≥ 50 years and post-menopausal women, using T score.

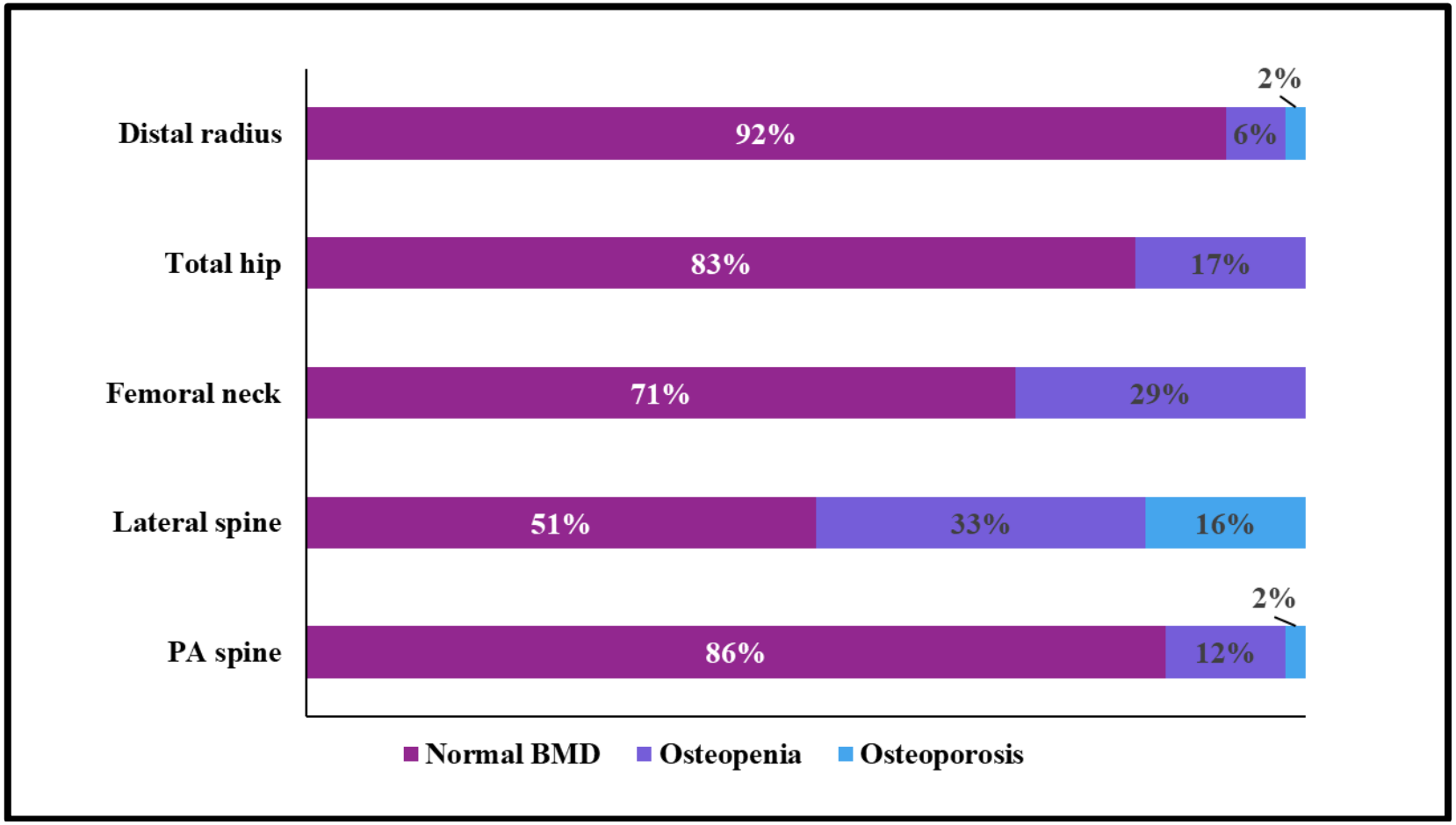
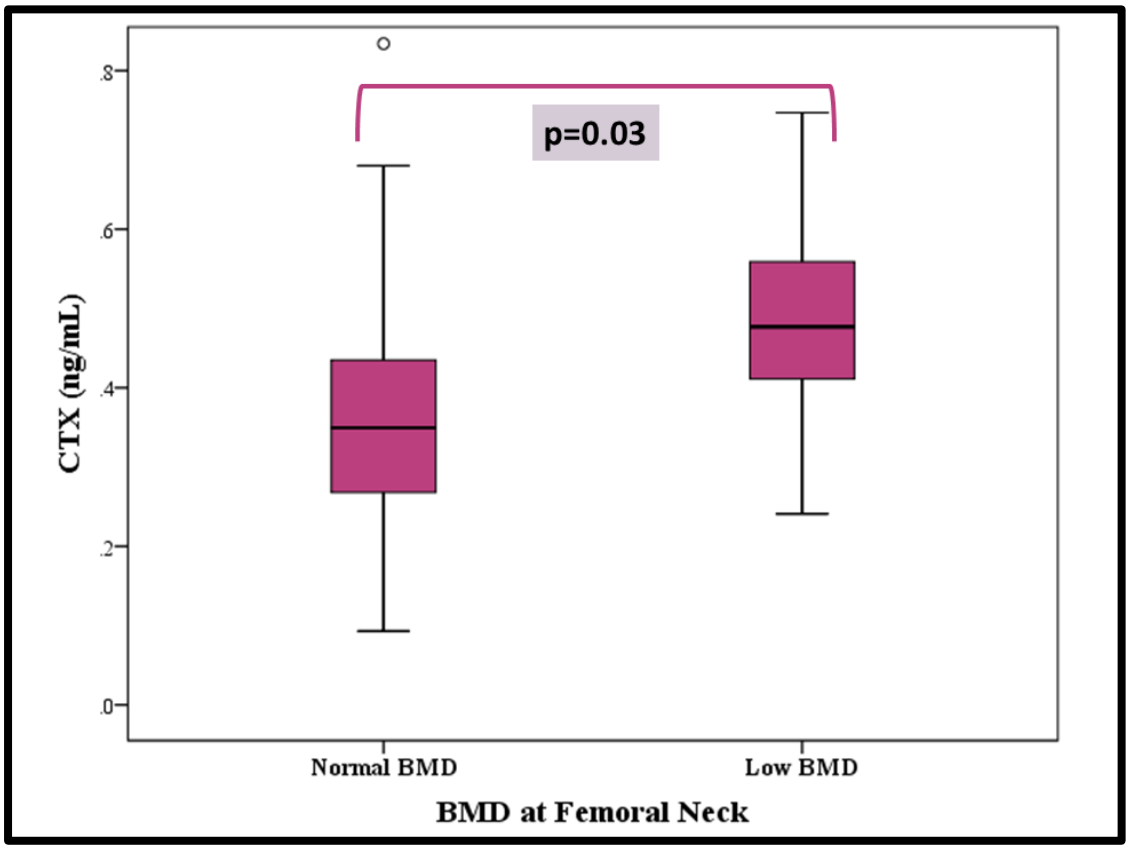
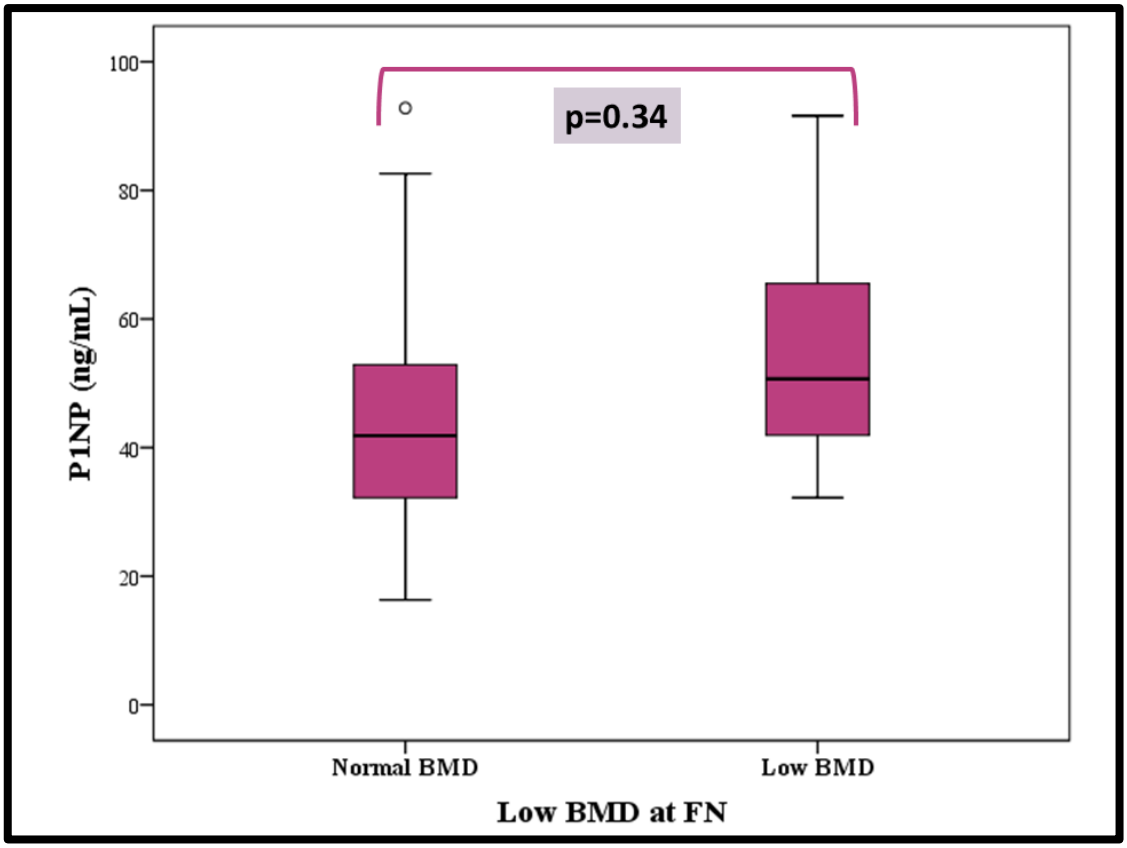


Figure 5-3: Comparison of bone turnover markers, (a) CTX, (b) P1NP and (c) osteocalcin, in participants with normal and low bone mineral density measured at the femoral neck. P<0.05 indicates statistical significance. BMD: Bone mineral density; CTX: C-terminal telopeptides of type 1 collagen; FN: femoral neck; P1NP: N-propeptide of type 1 collagen.

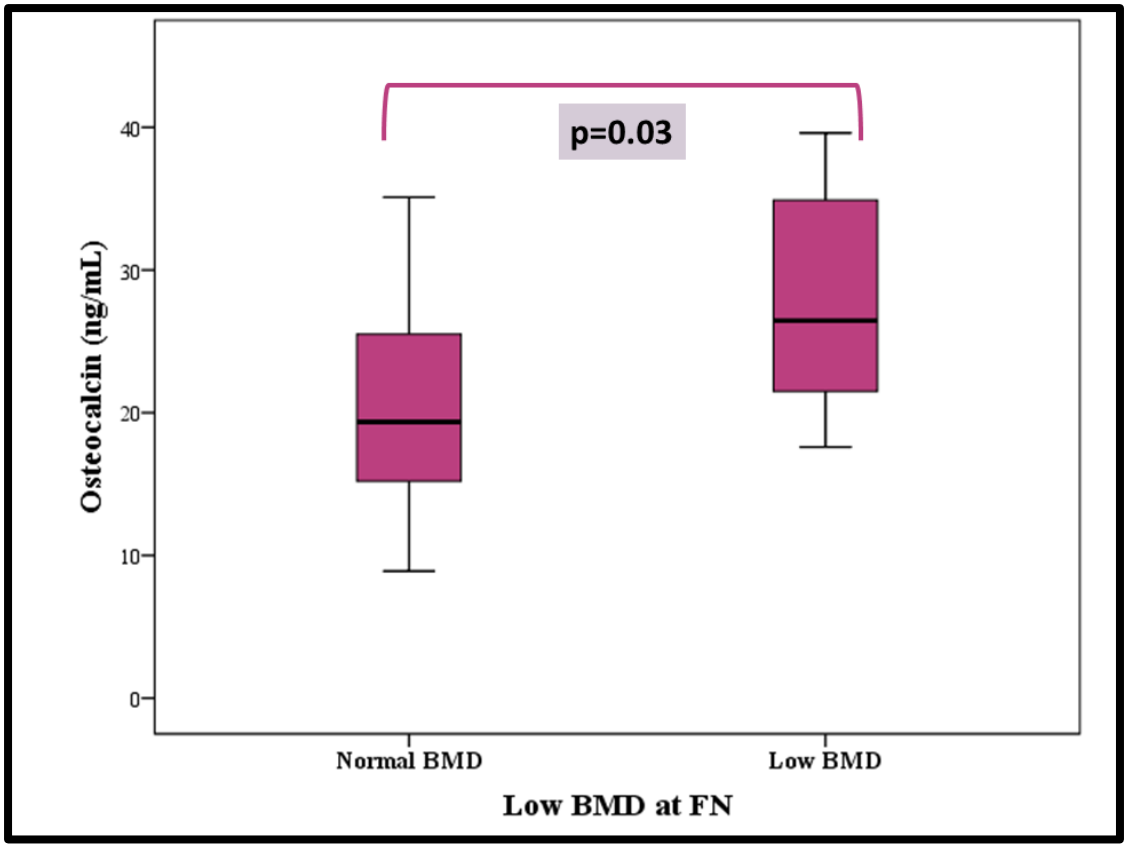
(a)



(b)



(c)


p=0.03
Osteocalcin (ng/mL)
40
30
20
10
0
Normal BMD
Low BMD
Low BMD at FN

Multiple regression analysis was performed, with femoral neck BMD as the dependent variable. Separate models were used to test the association of CTX and osteocalcin (log transformed) with femoral neck BMD, controlled for age, considering the known correlation between age and CTX. Both CTX and osteocalcin were associated with FN BMD, explaining 12% and 9% of the variance respectively (see Table 5-4). However, the model was adjusted further for potentially confounding variables: age; gender; presence of osteoporosis risk factors; BASDAI; current biologic treatment. The significant contributions of CTX and osteocalcin were subsequently lost.

Table 5-4: Multivariable analysis of the effect of BTMs on FN BMD.

	Variable	R^2	ß	95% CI	P value
Model 1	Log_{10}CTX	0.12	-0.17	-0.30 to -0.03	0.02
	Log_{10}Osteocalcin	0.09	-0.18	-0.35 to -0.00	0.05
Model 2	Log_{10}CTX	0.28	-0.10	-0.25 to 0.05	0.18
	Log_{10}Osteocalcin	0.26	-0.08	-0.27 to 0.10	0.37

Model 1: adjusted for age

Model 2: adjusted for age, gender, osteoporosis risk factors, BASDAI, current biologic treatment

BMD: Bone mineral density; BTM: bone turnover marker; CI: confidence interval; CTX: C-terminal telopeptides of type 1 collagen; FN: femoral neck.

BTMs in Z score population: men < 50 years & pre-menopausal women (n=48)

The prevalence of normal and low BMD in this subgroup is illustrated in Figure 5-4. There were no significant relationships between any of the BTMs and BMD at any site measured in this population. Additionally, there was no difference in BTM values between participants with and without fractures, fragility or otherwise.

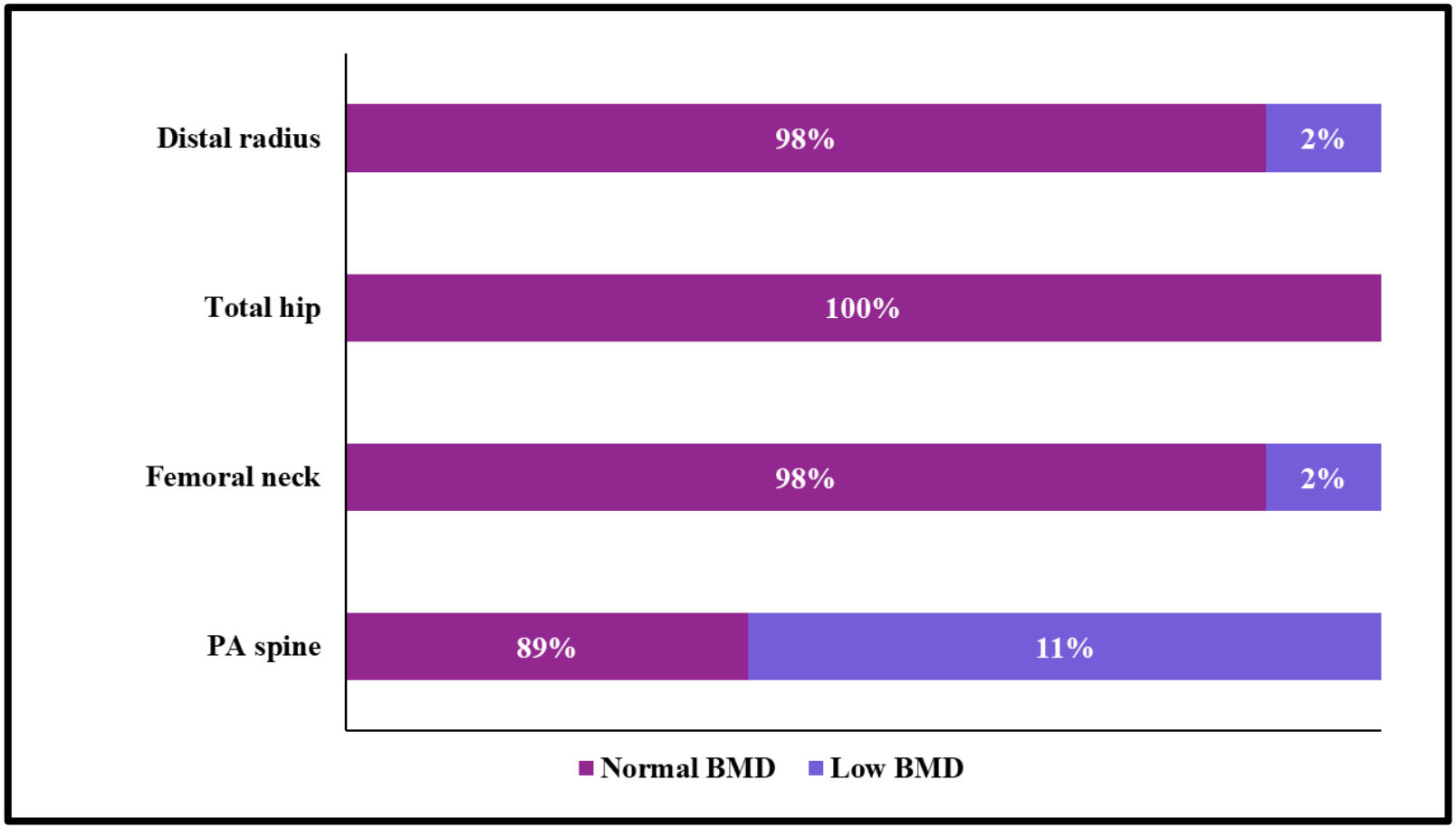
5.4.3 BTMs and osteoproliferation

Median (IQR) mSASSS was 8.5 (3.0 to 33.1) in the whole cohort, 12 (3.8 to 36.3) in males and 7 (2.2 to 11.8) in females, but the difference between genders was not significant (p=0.23). Median mSASSS was significantly higher in participants who fulfilled mNY criteria compared to those that did not (13.0 v 2.5, p<0.01) and BASRI-hip correlated positively with mSASSS (rho 0.31, p<0.01). PTH correlated positively with mSASSS (rho=0.25, p=0.01). There was no

correlation between mSASSS and CTX, osteocalcin or P1NP. There was also no significant relationship between BASRI-hip score and BTMs. MSASSS correlated with BMD of the lumbar spine when measured by PA projections of DXA (rho 0.34, $p<0.01$), but did not correlate with BMD at any other site.

Using the WHO T-score-applicable subgroup, participants with both osteoproliferation (mSASSS > 5, to exclude participants with erosions/sclerosis/squaring only) and low BMD (n=24) were compared to the rest of the cohort (n=27). There was no difference ($p>0.05$) in age, disease duration or delay to diagnosis between the two groups. Compared to those without, participants with both low BMD and osteoproliferation had a significantly higher CRP (10.4 v 4.3, $p=0.03$) and higher median P1NP (46.9 v 39.7, $p=0.04$); there was no significant differences in CTX or osteocalcin. There was a trend towards more active disease as measured by ASDAS-ESR (2.5 v 2.0, $p=0.07$), but there was no significant difference between groups in any disease outcome measure.

Figure 5-4: Prevalence of low BMD in men < 50 years and pre-menopausal women. Low BMD if Z score ≤ -2. Reference database not available to calculate Z scores for lateral lumbar spine.



5.4.4 Vitamin D

Median vitamin D was 62 (IQR 43 to 79). Thirty percent (n=30) of participants had insufficient levels of vitamin D as defined by the IOM, with seven participants deficient (7% of cohort) (see Table 5-1). Twenty-two participants (22.2%) were currently on vitamin D supplementation, with an additional 10.1% (n=10) previously on supplementation. Sixteen participants (16.2%) were currently taking calcium supplementation. Participants who never smoked had significantly higher levels of vitamin D than participants who currently or previously smoked (mean difference 17.5, 95% CI 3.1 to 31.8 nmol/L).

There was no difference in vitamin D levels between participants with and without low BMD at spine, hip or radius. There was no significant correlation between vitamin D and BTMs. Additionally, there was no relationship found between vitamin D and disease severity.

5.4.5 Testosterone

Descriptive data & associations with baseline characteristics

To examine the role of testosterone, females were excluded from the analysis (n=76). The mean (SD) age of the included men was 51.0 (11.8) years; disease duration 24.8 (12.5) years and delay to diagnosis 8.2 (8.3) years. In terms of disease severity, mean (SD) BASDAI was 3.7 (2.2); BASFI 3.7 (2.5); BASMI 4.2 (1.9); ASQoL 6.5 (5.0); HAQ 0.54 (0.50) and median (IQR) mSASSS was 12 (3.8, 36.3). Mean testosterone was 17.1 (6.5) nmol/L. There was no relationship between testosterone and age, disease duration or delay to diagnosis. Testosterone correlated inversely with BMI (r -0.42, $p<0.01$). In the participants with co-morbidities (78%, n=59), testosterone was significantly lower than those participants without co-morbidities (MD 3.73, 95% CI 0.23 to 7.23 nmol/L). Smoking had no effect on testosterone level. In addition, there was no difference in testosterone levels between those currently taking and not taking biologics.

BMD

Testosterone correlated negatively with PA spine BMD (r -0.29, p=0.01), but not with lateral spine, hip or radius BMD. There was no difference in mean testosterone levels in participants with and without low BMD. Testosterone correlated negatively with PTH (r -0.30, 0.01), but there was no relationship with CTX, P1NP or osteocalcin. Testosterone levels were lower in participants with a history of any prior fracture (mean difference 3.3, 95% CI 0.9 to 6.2). Participants with vertebral fractures had lower testosterone levels, but the difference did not reach statistical significance (mean difference 2.2, 95% CI -4.1 to 8.9).

Disease severity

Testosterone correlated inversely with several disease outcome measures: BASMI (r -0.36, p<0.01); BASFI (r -0.40, p<0.01); ASQoL (r -0.34, p<0.01); HAQ (r -0.35, p<0.01); ASDAS-ESR (r -0.29, p=0.01); ASDAS-CRP (r -0.29, p=0.01). Testosterone levels were lower in participants with active disease, defined as ASDAS-CRP>2.2 (MD 3.86, 95% CI 0.95 to 6.77). There was no relationship between testosterone and mSASSS (rho -0.20, p=0.09), CRP (r -0.21, p=0.07) or ESR (r -0.15, p=0.19).

Separate regression analyses were performed to investigate whether testosterone independently contributed to explaining disease severity. Testosterone significantly and independently contributed to explaining BASFI, HAQ and BASMI (Table 1-5). Lower testosterone was associated with a higher odds of active disease, or ASDAS-CRP>2.2 (OR 1.13, 95% CI 1.04 to 1.22). This association remained significant when adjusted for the variables outlined in Table 1-6 (OR 1.10, 95% CI 1.002 to 1.20).

Table 5-5: Multivariable analysis demonstrating associations between testosterone (independent variable) and measures of disease severity (dependent variables, individual models)

	Univariate			Multivariate*		
	ß	95% CI	P value	ß	95% CI	P value
BASDAI	-0.07	-0.15 to 0.01	0.08			
BASFI	-0.15	-0.24 to -0.07	<0.01	-0.09	-0.14 to -0.03	0.002
ASDAS-CRP	-0.045	-0.08 to -0.01	0.01	-0.03	-0.07 to 0.01	0.14
ASQoL	-0.26	-0.43 to -0.08	<0.01	-0.12	-0.25 to 0.18	0.09
HAQ	-0.03	-0.04 to -0.01	<0.01	-0.02	-0.03 to -0.00	0.02
BASMI	-0.11	-0.17 to -0.04	<0.01	-0.07	-0.12 to -0.01	0.02

**Controlled for age, BMI, current biologic use, BASDAI (except for model with ASDAS-CRP due to multicollinearity), blank cell indicates variable not included in model due to non-significance in univariable analysis. ASDAS: Ankylosing Spondylitis Disease Activity Index; ASQoL: Ankylosing Spondylitis Quality of Life; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CI: Confidence interval; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire.*

Table 5-6: Univariable and multivariable regression analysis, investigating association between testosterone and active disease, as measured by ASDAS-CRP>2.2

Analytic method	Active disease[a] OR (95% CI)
Unadjusted	1.13 (1.04 to 1.22)
Adjusted for age, BMI, current biologic use, presence of comorbidities	1.10 (1.002 to 1.20)

[a] defined as Ankylosing Spondylitis Disease Activity Score$_{CRP}$ > 2.2. BMI: body mass index; CI: Confidence interval; CRP: C-reactive protein; OR: Odds ratio.

5.4.6 Serum Urate (SUA)

Descriptive data

Median (25^{th}, 75^{th}) SUA was 314 μmol/L (262, 382), with 35% (n=34) of participants having a high SUA (>360 μmol/L). Males had higher median SUA than females (341 v 264 μmol/L, p<0.01). SUA correlated significantly with BMI (r=0.34, p<0.01). There was no significant correlation with age (r -0.13, p=0.22) or with mSASSS (rho 0.19, p=0.06).

BMD

SUA correlated significantly with BMD of the spine (AP r=0.28, p=0.01; lateral r=0.24, p=0.02), total hip (r=0.27, p=0.01) and forearm (distal third of forearm r=0.31, p<0.01; total forearm p=0.33, p<0.01; ultradistal forearm r=0.31, p<0.01). Participants with a high SUA had a significantly higher mean BMD at the spine (PA projection) (MD -0.10, 95% CI -0.17 to -0.01 μmol/L), total hip (MD -0.06, 95% CI -0.11 to -0.01 μmol/L) and distal third of forearm (MD -0.04, 95% CI -0.07 to -0.01 μmol/L). There was no difference in SUA level between participants with and without fragility fractures. Less participants with a high SUA had low BMD at lateral spine than those with a SUA level within the normal limits (25% versus 56%, χ^2 8.0, p=0.01). The differences at other sites were not significant.

In crude regression analysis with BMD as the dependent variable, SUA was significantly associated with AP spine BMD, lateral spine BMD, total hip BMD and forearm BMD. However, when adjusted for gender, BMI and age, SUA was no longer significantly associated with BMD at any site.

5.5 Discussion

5.5.1 Summary of findings: biomarkers and osteoporosis

The aim of this study was to assess the relationships between biomarkers and osteoporosis in individuals with axSpA. The biomarkers studied were BTMs (specifically CTX, P1NP and osteocalcin), vitamin D, SUA and testosterone. There were inverse relationships between BTMs and BMD at the hip (CTX, osteocalcin), spine (P1NP) and forearm (all three BTMs) in men over the age of 50 and in postmenopausal women, but not in younger men and pre-menopausal women. In men, testosterone was inversely correlated with BMD of the PA spine. Men with a previous history of fracture had lower testosterone levels than those without any history of a fracture. Increasing SUA was related to increasing BMD at the spine, hip and forearm. However, none of the biomarkers assessed in this study were independently able to explain low BMD in axSpA.

Bone turnover markers

Similar to the findings of this study, other studies have found correlations between high levels of bone resorption markers and low BMD in the femoral neck: Park et al (Park et al., 2008) demonstrated that urinary CTX-1 was inversely correlated with BMD at the femoral neck, and (Vosse et al., 2008) showed that urinary CTX-1 was inversely correlated with BMD of the hip (trochanter, not femoral neck). In contrast, two separate studies (Muntean et al., 2011, Gamez-Nava et al., 2016) found no relationship between serum CTX-1 and BMD at any site. However, Park et al (Park et al., 2008) provided no information regarding confounders. Vosse et al (Vosse et al., 2008) demonstrated that the correlation persisted when adjusted for disease duration, but no further adjustment was reported. Although simple correlation analysis in this study did similarly demonstrate significant relationships, what differentiates these results from existing literature is the additional control for potential confounders to test the independence of the relationship. The significant relationships were no longer significant once confounding variables were added, leading to the conclusion that there is no independent relationship between CTX and BMD of the femoral neck.

In terms of the comparability of this study with existing literature, many other studies used urinary CTX in their analysis, where we used serum samples of CTX. However, when collected correctly, serum CTX-1 samples are sufficiently stable to allow analysis (Szulc et al., 2017), with no evidence that urinary samples perform better (Huber et al., 2003). Therefore, our study is suitable for comparison with other studies which used urine samples.

This study also demonstrated no relationship between CTX and BMD of the lumbar spine, using either PA or lateral DXA assessment. Although this has been seen in previous studies (Muntean et al., 2011, Park et al., 2008), to our knowledge this is the first study which examined BTMs using lateral DXA of the spine. Therefore, we can be more confident that there is no relationship between bone resorption markers and BMD of the spine, as opposed to potentially missing a relationship due to the reduced ability of PA DXA to detect low BMD in the spine of axSpA, as outlined in Chapter 4.

The relationship between bone formation markers and BMD was also investigated and found that although both osteocalcin and P1NP correlate inversely with BMD, this relationship is lost once confounding variables are introduced. This lack of relationship has been demonstrated in a systematic review (Coiffier et al., 2013), but our study adds to the literature by confirming the lack of relationship when lateral DXA is used to assess BMD of the spine.

Therefore, we conclude that although inverse relationships do exist between bone turnover markers and BMD, they do not independently predict low BMD of the hip or spine in axSpA and are therefore not useful in predicting which participants are at risk of low BMD.

Vitamin D

Vitamin D was the second biomarker investigated in this study and no correlation was found, directly or indirectly, with low BMD at any site measured. Therefore, vitamin D levels were not clinically useful in predicting individuals who are at risk of low BMD. This confirms previous studies which similarly demonstrated that vitamin D does not relate to osteoporosis in axSpA (Mermerci Baskan et al., 2010, Arends et al., 2011, Klingberg et al., 2016). However, longitudinal studies are required to further define the role, if any, that vitamin D plays in the pathogenesis of low BMD.

Testosterone

Testosterone was the third biomarker investigated in this study, demonstrating no significant relationship with BMD in men, confirming the findings by Mitra et al (Mitra et al., 1999b). This finding conflicts with a study by Franck et al (Franck et al., 2004), which demonstrated that men with osteoporosis had lower testosterone than those with normal BMD; however, whether this represented an independent relationship is not presented in that manuscript. Testosterone levels were lower in participants with a history of a fracture at any point in their lifetime in this study; however, there was no relationship with fragility fractures, although it must be noted that the prevalence of fragility fractures in this cohort was low. In the ageing general population, lower testosterone levels have been clearly linked with an increased risk of fractures in men (Mohamad et al., 2016). Therefore, the finding that lower testosterone levels were present in men with a history of fracture is interesting, and further research in a cohort of men with a higher prevalence of fractures, particularly fragility fractures, is required.

Serum urate

We aimed to investigate the association between SUA levels and osteoporosis in adults with axSpA. Although SUA was significantly associated with BMD at spine, hip and forearm, this association was attenuated and lost statistical significance once controlled for gender, age and BMI. We also did not find any significant difference in SUA levels between participants with and without fragility fractures. However, it is worth stating again that the prevalence of fragility fractures in this cohort was low; therefore, it is possible that an association was simply not detected.

A meta-analysis highlighted that hyperuricaemia is associated with higher BMD and a reduced risk of fractures in the general population (Veronese et al., 2016). It has been hypothesised that the antioxidant properties of SUA may attenuate the high oxidative stress levels that can down-regulate osteoblastogenesis and characterise osteoporosis (Sendur et al., 2009, Yang et al., 2014, Ames et al., 1981, Almeida et al., 2007, Kellogg and Fridovich, 1977). Kang et al (Kang et al., 2015) investigated the association between SUA levels and BMD in a cross-sectional analysis of 150 participants in Seoul, Korea and reported that high SUA levels are associated with higher BMD at the lumbar spine, even when controlled for age, BMI, ESR and serum calcium concentrations. There was no association with SUA and BMD at the hip. However, there are important differences between the designs of the two studies, which limit the comparability: Kang et al studied males under the age of 50 only, whereas we included both genders and did not exclude based on age. The mean age of our cohort was 50 years, compared to 32 years in Kang's study. In addition, Kang used conventional PA DXA only in assessing BMD of the spine; 32% of the cohort had syndesmophytes, therefore it is theoretically possible that osteoproliferation prohibited accurate assessment of the BMD of the spine. The presence of syndesmophytes was not controlled for in the model assessing the association of SUA with BMD of the spine.

In summary, the results of this study indicate that although increasing SUA is associated with higher BMD of the spine, hip and forearm, it does not independently explain higher BMD levels in axSpA. This suggests that SUA cannot currently be used as biomarker for osteoporosis in this population.

5.5.2 Relationship between osteoporosis and osteoproliferation

A secondary aim of this study was to investigate the relationship between BMD and osteoproliferation using biomarkers. We demonstrated that participants with a combination of both low BMD and osteoproliferation had a significantly higher P1NP (marker of bone formation) than those participants who had (1) low BMD but no osteoproliferation, (2) osteoproliferation but normal BMD, or (3) neither low BMD nor osteoproliferation. There was no similar finding with CTX or osteocalcin. We also demonstrated that CRP was higher in participants with both, with a trend towards more active disease. This suggests that increased bone formation and more active disease are related to the co-existence of low BMD and structural damage. However, the results of this study need to be interpreted with caution, as it is a cross-sectional study, so causation cannot be determined. Further exploration of this finding is warranted, as it may shed light on the pathophysiology linking low BMD and osteoproliferation.

5.5.3 Biomarkers and disease activity

The final aim of this study was to assess the role of biomarkers in disease activity. Although we did not detect any definite link between testosterone and bone health, we did demonstrate that lower testosterone levels independently predicted active disease, higher BASMI, worse quality of life and more disability in men. To our knowledge, this is the first study in axSpA that has demonstrated this finding.

Testosterone has long been postulated to play an immunoregulatory role in autoimmune disease. The presence of testosterone inhibits the secretion of proinflammatory cytokines, such as TNF and IFNɣ (Janele et al., 2006). In mice, testosterone was protective against the development of arthritis (Keith et al., 2013). Lower levels of testosterone predicted the development of rheumatoid factor-negative rheumatoid arthritis in a case-control study of 104 cases (Pikwer et al., 2014). In a separate longitudinal observational study (Tengstrand et al., 2009), participants with early RA (<1 year) had lower testosterone levels than controls. Participants at two years with controlled disease had improved testosterone levels, which were significantly higher than participants with sustained activity. However, causation could not be established in the observational study, therefore whether low testosterone contributed to the risk of RA or was a consequence of the disease path is unknown. In a longitudinal study of hypogonadal men with Crohn's disease, testosterone replacement therapy reduced disease activity, with no change seen in hypogonadal men not treated with testosterone (Nasser et al., 2015).

In AS, early studies appeared to demonstrate that testosterone levels were higher in participants compared to healthy controls (Masi, 1992). However, more recent literature disputes this (Giltay et al., 1999, Straub et al., 2002), and the use of phenylbutazone (NSAID) has been reported to interfere with the testosterone assay, leading to falsely elevated levels (Giltay et al., 1998). One small study found that treating nine participants with severe AS with human chorionic gonadotrophin injections improved oestradiol levels and reduced ESR (Tapia-Serrano et al., 1991).

Based on the available evidence, it is biologically plausible that lower testosterone levels in axSpA would lead to more active disease. To our knowledge, this is the first study which demonstrates that lower testosterone is associated with more severe disease, even when controlling for important confounding variables. Whether testosterone levels change if a person moves from active to inactive disease is unknown. In addition, the effect of testosterone replacement therapy on disease activity in axSpA is unknown. More research is required, in

particular longitudinal studies to determine whether low testosterone is a cause of or a consequence of axSpA.

5.5.4 Limitations

The cross-sectional design of this study only allows us to explore associations and prohibits any comment on causality. However, with this cross-sectional study, we identified a number of interesting findings, allowing research questions to be drafted that can be subsequently tested in longitudinal analysis. Selection bias cannot be out-ruled in this study, as the participants attending clinics in St. James's Hospital and Tallaght Hospital may not be representative of all adults with axSpA. A further limitation is that bone turnover marker samples, particularly CTX-I, need to be collected under strict conditions and it is theoretically possible that not all samples taken complied fully with these conditions; however, to minimise this risk, all participants were educated prior to enrolling in the study and compliance with the conditions was assessed prior to taking the sample. The prevalence of fragility fractures in this study was low, therefore the power to detect relationships was low. Finally, this study was performed in a cohort of predominantly male Caucasian adults with axSpA; extrapolation of the results to other populations must be performed with caution. In particular, the findings need to be replicated in cohorts with more adult women, an issue common to many axSpA studies, due to the historic under-recognition of the condition in women.

5.6 Conclusion

In this cross-sectional analysis, increasing BTMs correlated with lower BMD at the hip and spine in adults with axSpA. However, the relationship between BTMs and BMD was attenuated once confounders were introduced. There was no relationship between vitamin D or testosterone and BMD in axSpA. Higher serum urate was associated with higher BMD at the spine and hip; however, the relationship was lost once the effect of age, gender and BMI was introduced. Therefore, none of the biomarkers tested in this observational study were useful as clinical biomarkers for osteoporosis in this population.

This is the first study to demonstrate that lower testosterone levels in men with axSpA independently predicted active disease, as well as higher BASMI, worse quality of life and more disability. These findings need to be replicated, then explored further in a longitudinal analysis, to determine the cause-effect pattern.

Chapter 6 Quantitative ultrasound of the heel – suitable for triage?

Material from this chapter has been disseminated in the following publication:

Fitzgerald GE, Anachebe T, McCarroll KG, O'Shea FD. (2020) Calcaneal quantitative ultrasound has a role in out ruling low bone mineral density in axial spondyloarthropathy. *Clinical Rheumatology*. Jan 17. doi: 10.1007/s10067-019-04876-9. [Epub ahead of print].

(full manuscript in Appendix A).

6.1 Introduction

DXA is the gold standard for assessing BMD and is an important tool in the subsequent diagnosis or exclusion of osteoporosis (Shepherd et al., 2015). It is also the recommended method to monitor changes in BMD (Shepherd et al., 2015). This non-invasive technique is now in widespread clinical use. However, as outlined in the cross-sectional study of ASRI in Chapter 2, only a minority of adults with axSpA in Ireland had ever undergone DXA assessment of their BMD. This suggests that the systematic assessment of bone health is suboptimal in this population. Considering the high prevalence of low BMD demonstrated in both the analysis of ASRI in Chapter 2 and the cross-sectional study in Chapter 4, there is a real need to improve our assessment of BMD in adults with axSpA.

There are several potential explanations for the low levels of assessment of BMD in this population. One potential contributing factor is that as the general population is ageing (European Commission, 2018), the demand for a comprehensive assessment of bone health, including DXA assessment, is growing. This can result in reduced access to DXA, with long waiting times. Another reason more specific to axSpA is that less than a third of rheumatologists indicated that assessing for osteoporosis was part of their routine management for adults with AS (Bessant et al., 2003). Part of this may be due to the historic under-recognition of AS in women, with the belief that the risk of osteoporosis is low in men. This belief is not backed up the literature, considering the high prevalence detected in cohorts of predominantly male adults with axSpA

(Chapters 3 & 4). Due to the interplay of these contributing factors, osteoporosis is under-recognised in adults with axSpA.

A pre-screening tool to identify an individual's risk of having osteoporosis would be helpful in reducing the burden on DXA. DXA assessment could be delayed if clinicians could confidently categorise an individual as low risk for having osteoporosis. Pre-screening strategies could also identify individuals at very high risk of having osteoporosis, allowing treatment to be commenced prior to DXA assessment. Thus, pre-screening tools for osteoporosis would allow clinicians to risk-stratify individuals, reducing the need for unnecessary DXA assessment. This would ensure that available resources are being used appropriately, reserving DXA for individuals at intermediate risk who require a definitive assessment of their BMD with DXA.
Quantitative ultrasound (QUS) of the calcaneus is a potential triage tool for osteoporosis. It has many advantages over DXA: it does not contain any ionising radiation, it is portable, it is non-invasive. The calcaneus is the only site recognised by the ISCD as suitable for QUS assessment of bone health (Schousboe et al., 2013). QUS generates two parameters: the speed of sound (SOS) and broadband ultrasound attenuation (BUA) (Chin and Ima-Nirwana, 2013). The stiffness index (SI) is a composite measure of SOS and BUA, which some researchers suggest is more useful in determining people with low bone health (Guglielmi and de Terlizzi, 2009). The use of the same T-score cut-offs as DXA to quantify normal BMD, osteopenia and osteoporosis are not recommended by the ISCD as they employ different techniques to assess bone health (Shepherd et al., 2015). Instead, device-specific cut-offs are needed (Chin and Ima-Nirwana, 2013).

There are different ways in which new tests can be introduced to the management of individuals – it can be intended to replace the original test, it can be used in combination with the existing test to improve the accuracy of diagnosis ('add-on') or it can be used as a triage test, where the result of the new test will be used to determine whether a person needs to undergo the reference test (Hayen et al., 2010).

QUS of the calcaneus has been shown to predict fractures in postmenopausal women and men over 65 years (Shepherd et al., 2015). A systematic review demonstrated that QUS of the calcaneus was potentially useful as a pre-screen tool in the assessment of osteoporosis, using device-specific thresholds (Thomsen et al., 2015). There is conflicting literature regarding the use of QUS in axSpA. Speden et al (Speden et al., 2002) investigated the role of QUS in 23 women with axSpA and found no consistent correlation between QUS and BMD of the hip or spine. However, in contrast Jansen et al (Jansen et al., 2003) found QUS performed similarly to DXA in detecting individuals with osteoporosis-related fractures. The role of QUS as a pre-screening tool for osteoporosis in adults with axSpA has not been examined.

Although the fracture prediction ability of QUS of the calcaneus is equal to or even superior to DXA (Meszaros et al., 2007, Gonnelli et al., 2005), the lack of diagnostic criteria and lack of evidence that treatment based on QUS parameters is effective prohibits the replacement of DXA with QUS (Thomsen et al., 2015). However, access to QUS as a triage test would reduce the demand on DXA, by limiting the number of individuals who need to undergo the reference test.

6.2 Aims

The aims of this study were to:

1. Determine whether QUS parameters correlate with BMD in adults with axSpA, including lateral DXA assessment of the spine
2. Explore the use of QUS as a pre-screening tool to detect participants at **low-risk** of having *low BMD* as defined by the WHO criteria (1993), using thresholds with 90% sensitivity
3. Explore the use of QUS as a pre-screening tool to detect participants at **high-risk** of having *osteoporosis* as defined by the WHO criteria (1993), using thresholds with 90% specificity
4. Explore the use of QUS as a pre-screening tool to detect participants at **high-risk** of having *low BMD* as defined by the WHO criteria (1993), using thresholds with 90% specificity
5. Assess the ability of QUS to reduce the number of participants requiring DXA assessment of their bone health

6.3 Methods

6.3.1 Study design, setting & population

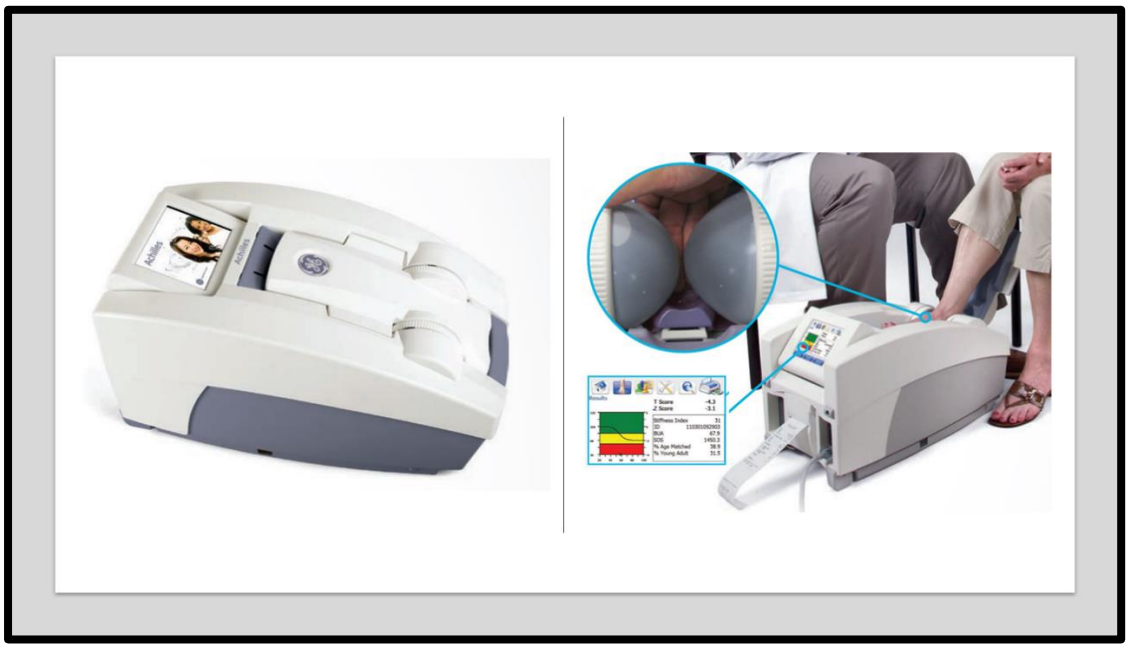
The methods for this study have been outlined in detail in Chapter 4, Section 4.3. This was an observational, cross-sectional, twin-centre study, which took place between April 2017 and January 2018. The population was adults with axSpA according to the ASAS criteria. Participants were recruited as outlined in Section 4.3.2. Participants with a history of current or past treatment with osteoporosis treatment, defined as anti-resorptive medication (bisphosphonates, denosumab), anabolic medication (teriparatide) or strontium ranelate, were excluded; pre-menopausal women and men under the age of 50 years were also excluded, as defined by the WHO criteria (1993).

6.3.2 Data collection

The data collection methods for this study are outlined in detail in Section 4.3. A detailed standardised assessment was performed on all participants, which included demographic and clinical information. BMD was assessed using DXA as outlined in Section 4.3.5.

QUS of the right calcaneus was assessed using the General Healthcare (GE) Lunar Achilles InSight Densitometer (Figure 6-1). The participant sat on a stable chair in front of the machine, with a bare foot. The leg was positioned to ensure that the foot and calf were aligned with the calf support and the foot was positioned firmly in the machine against the footplate. The participant was instructed to remain still during the measurement. The heel was surrounded by warm water, which was contained within inflated membranes. The transducer on one side of the heel passed a sound wave through the water-filled membranes and heel, which was detected by a transducer on the other side of the heel (GE Healthcare, 2011). Daily calibration was performed, in accordance with the manufacturer's instructions. The following parameters were obtained for each individual: SOS, BUA, SI, T score.

Figure 6-1: Demonstration of use of GE Lunar Achilles InSight densitometer.



6.3.3 Thresholds for QUS measurements

Our pre-screening approach aimed to identify an upper QUS threshold measurement, **above** which there was a 90% certainty, or sensitivity, that a participant **did not** have low BMD. We considered low BMD instead of osteoporosis as our target, as although the risk of fracture is highest in those with osteoporosis, most fractures occur in people with osteopenia (Compston et al., 2019); therefore, we felt it important to capture individuals with low BMD, not just osteoporosis. A high sensitivity was required to reduce the number of participants mis-classified as low risk of having low BMD i.e. false negatives. Participants with QUS measurements which were above this threshold were deemed as *low risk for low BMD,* thus not requiring DXA assessment. This was the 'low-risk triage approach'.

We also aimed to identify a lower QUS threshold measurements, **below** which there was a 90% certainty, or specificity, that a participant had osteoporosis. A high specificity was chosen to reduce the risk of participants mistakenly being classified as osteoporosis (false positive). Although participants with QUS measurements below this threshold would require onward referral for DXA assessment to establish a baseline BMD, they should be considered for treatment prior to DXA assessment, thus reducing delays. This was the 'high-risk triage approach'.

Lastly, we aimed to identify a QUS threshold measurement, **below** which there was a 90% certainty, or specificity, that a participant had low BMD. A high specificity was chosen to reduce the risk of participants mistakenly being classified as low BMD (false positive). Although individuals in this group would require DXA assessment before commencing pharmacological treatment, non-pharmacological measures to improve bone health could be employed while awaiting DXA. This was the 'intermediate-risk triage approach'.

6.3.4 Statistical analysis

Descriptive statistics are presented as frequencies with percentages and mean with standard deviation (SD) or median with 25^{th} and 75^{th} percentiles, as appropriate, for categorical and continuous variables respectively. Relationships between continuous variables were assessed using Pearson's correlation coefficients (r) for normally distributed variables or Spearman's correlation coefficients (rho) for non-normally distributed variables. This correlation analysis was used to determine the strength and direction of relationships between QUS parameters and BMD at each site. Independent two-tailed T-tests (two groups) or Analysis of Variance (ANOVA; three or more groups) were used to explore differences between groups in continuous data for normally

distributed data. Mann-Whitney U-test or Kruskall-Wallis tests were the equivalent non-parametric tests. Chi-square tests were used to compare categorical variables.

Receiver operating characteristics (ROC) curve analysis was used to determine the discriminative ability of QUS. Each parameter of QUS (SOS, BUA, SI, T-score) was tested individually for its ability to discriminate between osteoporosis or low BMD and normal BMD at the PA spine, lateral spine, total hip, femoral neck, hip/spine combined. Data is presented as Area Under the Curve (AUC), with 95% CI. The difference between the AUC and BMD by DXA was tested using a two-sided test, with a p-value of <0.05 considered significant. Any parameters without significant discriminative ability were excluded from further analysis. Using the ROC analysis, we determined the absolute threshold value for each parameter which identified participants with low BMD (low-risk triage strategy) or osteoporosis (high-risk triage strategy), using the sensitivity and specificity values as outlined in Section 6.3.3. Using these threshold values, we calculated positive predictive values (PPV) and negative predictive values (NPV). For the low-risk triage strategy, the number of DXAs saved using this approach was calculated as (true negatives + false negatives)/(true positives + false positives + false negatives + true negatives). The number of participants misclassified was calculated as false negatives/(true positives + false positives + false negatives + true negatives) (Thomsen et al., 2015).

A p-value of <0.05 was considered statistically significant for all analyses. IBM SPSS version 24 was used for statistical analysis.

6.4 Results

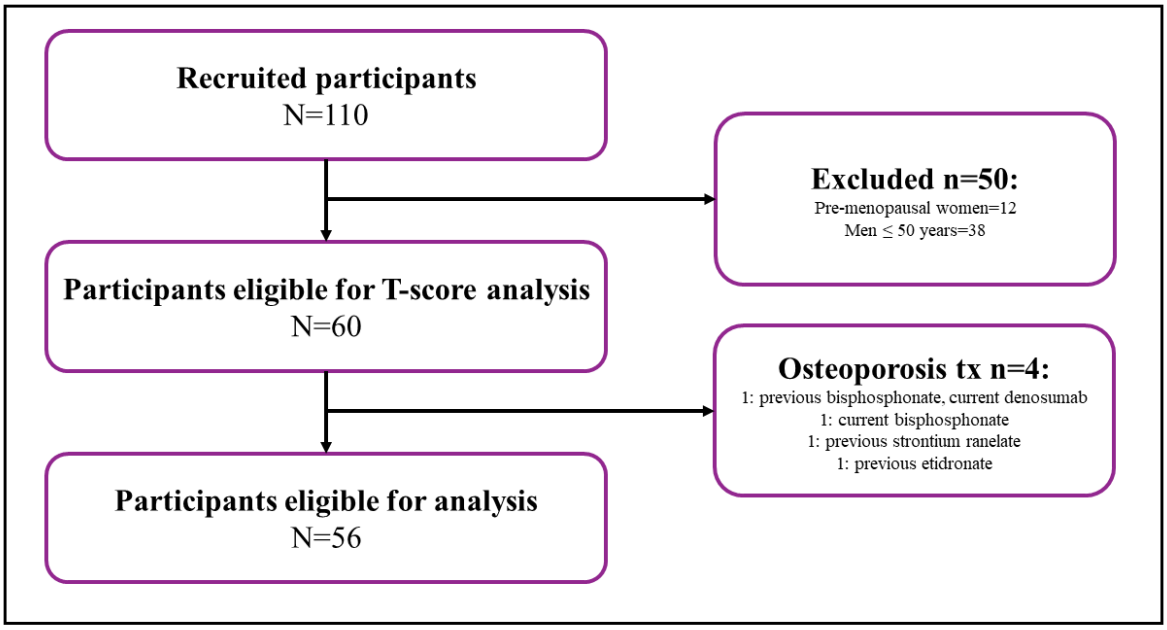
6.4.1 Participant characteristics

Of the 110 recruited participants, 56 participants were included in this sub-analysis (see Figure 6-2). Table 6-1 outlines the baseline demographic and clinical characteristics of the cohort, of whom 77% were male and the average (SD) age was 58 (7.2) years. The prevalence of low BMD (T score <-1.0) was 13% (n=7) at PA spine, 45% (n=24) at lateral spine, 15% (n=8) at total hip and 30% (n=16) at femoral neck. Fifty-six percent (n=30) of the cohort had low BMD affecting at least one site. The prevalence of osteoporosis (T score ≤ -2.5) was 2% (n=1) at PA spine, 15% (n=8) at lateral spine, 0% (n=0) at the hip).

6.4.2 Correlation analysis between QUS parameters and BMD

The mean and standard deviation for each parameter is outlined in Table 6-1. BUA correlated significantly with BMD at the PA spine, lateral spine and femoral neck; SI correlated with BMD at the PA and lateral spine, plus femoral neck; T score correlated with PA spine and femoral neck; SOS did not correlate with BMD at any site (see Table 6-2).

Figure 6-2: Flow-chart of participants eligible for analysis.



6.4.3 ROC curve analysis: discriminant ability of each QUS parameter to detect low BMD and osteoporosis

ROC analysis was used to determine which QUS parameters were able to discriminate between participants with and without low BMD at each site measured by DXA (see Figure 6-3). All QUS parameters had the ability to discriminate between a diagnosis of low and normal BMD, with the AUC varying from 0.695 to 0.779. BUA displayed the greatest ability to discriminate between cases and controls (see Table 6-3). The discriminative ability of all QUS parameters to detect low BMD at each site assessed is outlined in Table 6-3; none of the QUS parameters had the ability to identify cases of low BMD at total hip or PA spine.

All QUS parameters were unable to discriminate between osteoporosis and controls or between vertebral fractures and controls ($p>0.05$ for AUC). However, there was a small number of cases of osteoporosis (n=8) and vertebral fractures (n=3) in this cohort.

Table 6-1: Baseline demographic and clinical characteristics for cohort.

Variable	Whole population (n=56)
Male	43 (77)
Age, *years*	58.0 (7.2)
Caucasian	54 (96)
Disease duration, *years*	32.4 (12.5)
Delay to diagnosis, *years*	8.0 (10.6)
Smoking status	
Current	14 (25)
Past	25 (45)
Never	17 (30)
HLA-B27 positive	42 (78)
BMI, *kg/m^2*	28.4 (4.7)
mNY criteria	53 (95)
Treatment	
Current biologic use	28 (50)
Disease severity†;	
BASMI	5.4 (4.0, 6.4)
BASDAI	3.9 (2.3, 5.8)
ASDAS-CRP	2.4 (1.6, 3.2)
ASDAS-ESR	2.1 (1.5, 2.9)
BASFI	4.7 (2.6, 6.6)
ASQoL	7.0 (3.5, 12.0)
HAQ	0.63 (0.3, 1.3)
mSASSS	26.5 (7.8, 58.8)
QUS parameters	
SOS (m/s)	1554.4 (43.5)
BUA (dB/MHz)	111.4 (14.5)
SI	89.4 (17.3)
T-score	-0.8 (1.3)
BMD by DXA, *g/cm^2*	
PA spine	1.13 (0.21)
Lateral spine	0.74 (0.15)
Femoral neck	0.79 (0.11)
Total hip	0.95 (0.11)

Mean (SD) or n (%), unless otherwise stated. †median (25th, 75th percentiles); ASDAS: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis Quality of Life; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BMI: body mass index; BUA: broadband ultrasound attenuation; CRP: C-reactive protein; DXA: dual-energy x-ray absorptiometry; ESR: erythrocyte sedimentation rate; HAQ: Health assessment questionnaire; HLA: human leucocyte antigen; mNY: modified New York; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; PA: posterior-anterior; QUS: quantitative ultrasound; SD: standard deviation; SI: stiffness index; SOS: speed of sound.

Table 6-2: Correlation matrix, demonstrating associations between quantitative ultrasound parameters and bone mineral density.

BMD site†	QUS parameters			
	BUA	*SOS*	*SI*	*T score*
PA spine BMD	**0.503***	0.203	**0.418***	**0.407***
Lateral spine BMD	**0.349***	0.151	**0.296***	0.273
Femoral neck	**0.515***	0.069	**0.329***	**0.312***
Total hip	**0.482***	0.016	0.271	0.260

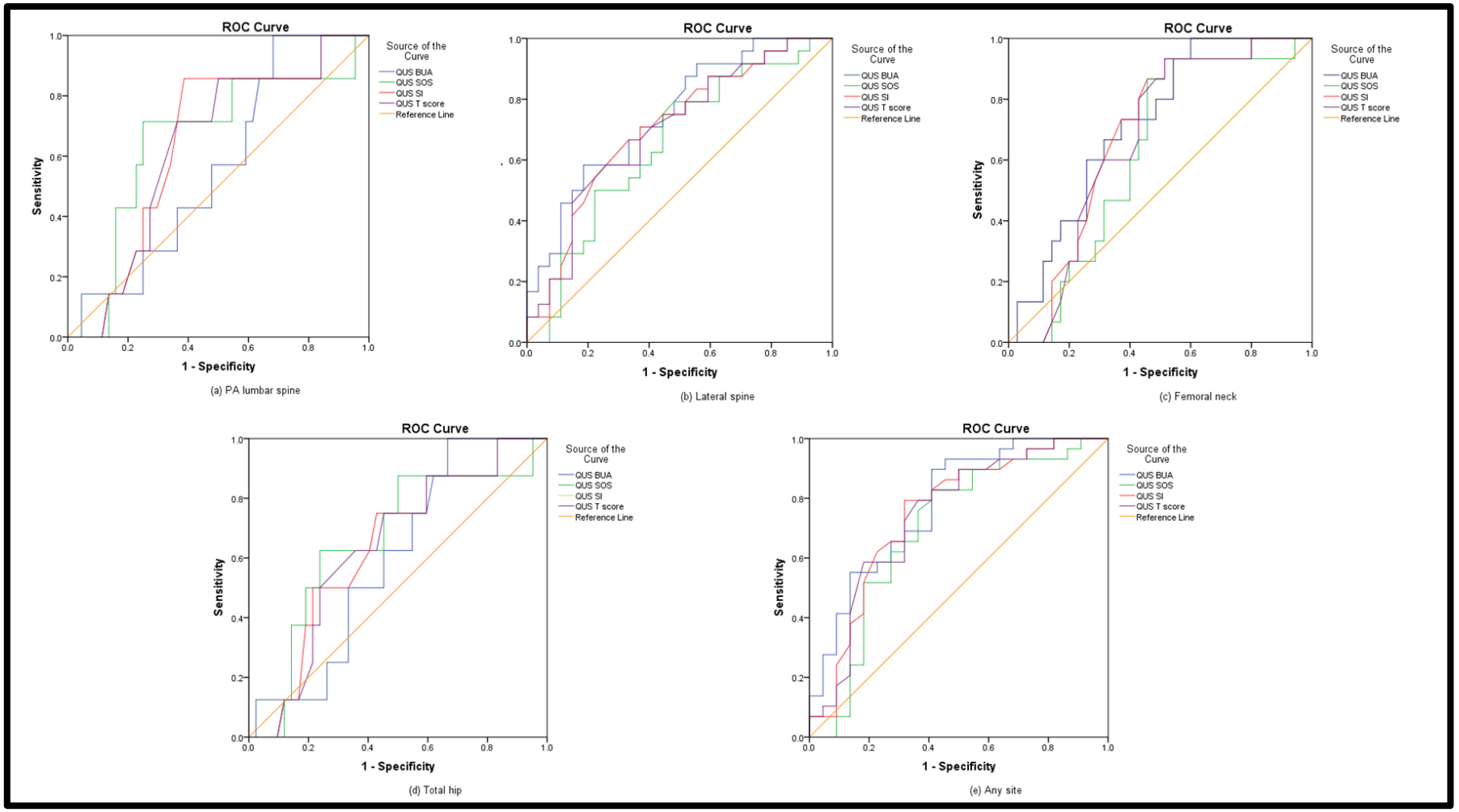
**denotes p<0.05. Significant values highlighted in bold. †Measured by DXA. BUA: broadband ultrasound attenuation; PA: posterior-anterior; SI: stiffness index; SOS: speed of sound;*

Table 6-3: Discriminative ability of quantitative ultrasound to diagnose low bone mineral density (BMD). Low BMD is defined as T score < -1 (Shepherd et al., 2015).

Site	Variable	AUC†	P value	95% CI†
Any site†	SOS	0.695	**0.02**	**0.538 to 0.852**
	BUA	0.779	**0.001**	**0.649 to 0.909**
	SI	0.747	**0.003**	**0.604 to 0.890**
	T score	0.742	**0.003**	**0.599 to 0.885**
PA spine	SOS	0.653	0.20	0.425 to 0.880
	BUA	0.567	0.58	0.375 to 0.758
	SI	0.648	0.21	0.456 to 0.840
	T score	0.633	0.26	0.439 to 0.827
Lateral spine	SOS	0.647	0.07	0.494 to 0.801
	BUA	0.746	**0.003**	**0.613 to 0.879**
	SI	0.704	**0.01**	**0.561 to 0.848**
	T score	0.697	**0.02**	**0.552 to 0.841**
Total hip	SOS	0.658	0.16	0.449 to 0.866
	BUA	0.597	0.39	0.420 to 0.774
	SI	0.638	0.22	0.447 to 0.829
	T score	0.635	0.23	0.446 to 0.825
Femoral neck	SOS	0.623	0.17	0.465 to 0.781
	BUA	0.718	**0.02**	**0.577 to 0.859**
	SI	0.682	**0.04**	**0.534 to 0.830**
	T score	0.669	0.06	0.519 to 0.818

†Low BMD in at least of any hip and/or any spine site measured. Significant values highlighted in bold. AUC: area under the curve; BUA: broadband ultrasound attenuation; CI: confidence interval; PA: posterior-anterior; SI: stiffness index; SOS: speed of sound.

Figure 6-3: Receiver operating characteristics (ROC) curves for each QUS parameter (BUA, SOS, SI, T score) as screening tools for detecting low BMD at (a) PA lumbar spine, (b) lateral spine, (c) femoral neck, (d) total hip, and (e) any site.



6.4.4 Cut-off values for 'low-risk triage approach'

The ability of QUS to detect low BMD at any site (all four parameters), lateral spine (BUA, SI, T score) and femoral neck (BUA and SI) was studied further (see Table 6-4). The remaining sites (total hip, PA spine) were not studied, due to the inability of QUS to discriminate between cases and controls at those. The BUA parameter with a cut-off of 117.65 had a sensitivity of 93%, specificity of 55%, PPV of 73% and NPV of 86% for ruling out a diagnosis of low BMD. The SI parameter with a cut-off of 106 had a sensitivity of 93%, specificity of 32%, PPV of 64% and NPV of 78% in ruling out low BMD. The T score cut-off of 0.45 had a sensitivity of 93%, specificity of 36%, PPV of 66% and NPV of 80% in ruling out low BMD at either hip or spine. Using this pre-screening strategy, whereby participants with values above the threshold were considered low-risk of low BMD and could have avoided DXA assessment, between 19 and 30% of DXAs could have been saved, with only 4% of participants misclassified. Table 6-4 outlines similar data for out-ruling low BMD at femoral neck and lateral spine individually, using cut-offs chosen which give the required sensitivity of at least 90% i.e. the cut-off above which participants have a low risk of low BMD.

6.4.5 Cut-off values for 'high-risk triage approach'

Only eight cases of osteoporosis (T score $\leq$-2.5) were detected in this cohort. As QUS parameters were unable to discriminate between osteoporosis and controls (Section 1.4.3), cut-off values for a 'high-risk' approach, whereby individuals could be confidently assessed as having osteoporosis without a DXA, could not be established.

6.4.6 Cut-off values for 'intermediate-risk triage approach'

In the 'low-risk' approach detailed previously, we identified a threshold above which we could out-rule low BMD with 90% confidence. In this intermediate-risk approach, we aimed to identify a threshold below which participants have a high risk of low BMD, using a pre-defined specificity of greater than 90%. Using BUA parameter, we found that a threshold of 102.9 had a sensitivity of 41%, specificity of 91%, PPV of 78% and NPV of 60% to detect low BMD (see Table 6-5). Using SI parameter, a threshold of 75.5 had a sensitivity of 24%, specificity of 91%, PPV of 67% and NPV of 57% in detecting low BMD. A T score threshold of -1.9 had a sensitivity of 17%, specificity of 91%, PPV of 78% and NPV of 55%. See Table 6-5 for equivalent data for spine and hip individually.

Table 6-4: 'Low-risk triage approach', using QUS, i.e. threshold above which participants have low risk of low bone mineral density (90% sensitivity).

Site	Variable	Threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	DXAs avoided (%)*	Misclassification rate (%)[$]
Any site	BUA	117.65	93	55	73	86	27	4
	SOS	1591.5	93	36	66	80	20	4
	SI	106	93	32	64	78	18	4
	T score	0.45	93	36	66	80	20	4
Lateral spine	BUA	117.65	92	44	59	86	27	4
	SI	106	92	30	52	78	18	4
	T score	0.45	92	30	54	80	20	4
Femoral neck	BUA	114.65	93	46	42	94	34	2
	SI	93.5	93	49	44	94	36	2

**calculated as TN + FN/TP + FP + FN + TN.* [$] *Calculated as FN/TP + FP + FN + TN.*

BUA: broadband ultrasound attenuation; DXA: dual-energy x-ray absorptiometry; FN: false negative; FP: false positive; NPV: negative predictive value; PPV: positive predictive value; QUS: quantitative ultrasound; SI: stiffness index; SOS: speed of sound; TN: true negative; TP: true positive.

Table 6-5: 'Intermediate-risk triage approach', i.e. threshold below which participants have high risk of low BMD (90% specificity).

Site	Variable	Threshold	Sensitivity (%)	Specificity (%)	PPV	NPV
Any site	BUA	102.9	41	91	78	60
	SOS	1509.5	69	91	50	53
	SI	75.5	24	91	67	57
	T score	-1.9	17	91	75	55
Lateral spine	BUA	100.1	29	93	78	60
	SI	72.5	21	93	71	57
	T score	-1.9	21	93	71	57
Femoral neck	BUA	99.0	13	91	40	71
	SI	69.5	0	91	0	68

BUA: broadband ultrasound attenuation; NPV: negative predictive value; PPV: positive predictive value; QUS: quantitative ultrasound; SI: stiffness index; SOS: speed of sound.

6.5 Discussion

The aim of this study was to determine the suitability of QUS of the calcaneus as a triage tool in the screening of postmenopausal women and men over the age of 50 years with axSpA for osteoporosis. Within this, three separate strategies were tested: (1) determine a threshold **above** which participants would be deemed as low risk for having low BMD (i.e. low BMD out-ruled), negating the need for a DXA assessment; (2) determine a threshold **below** which participants would be identified as at high risk of having osteoporosis, and treatment initiation could be considered in the absence of a DXA; (3) determine a threshold **below** which participants are considered at high risk of having low BMD, and in the absence of other factors, non-pharmacological measures could be considered to improve bone health, while awaiting DXA assessment.

Existing literature investigating the usefulness of QUS as an alternative to DXA uses the ability to detect osteoporosis as the discriminator (Clowes et al., 2006, Zha et al., 2015, Thomsen et al., 2015). However, in this study, we chose to investigate the ability of QUS to discriminate between a diagnosis of low and normal BMD, rather than between a diagnosis of osteoporosis and not-osteoporosis. One of the purposes of this study was to investigate if QUS could identify low-risk individuals, who could therefore avoid DXA assessment. Although the risk of fracture is highest in individuals within the osteoporotic range, most fractures in the general population occur in individuals who have a T-score within the osteopenic, rather than osteoporotic, range (Compston et al., 2019). It is important to identify people with low BMD, not only with overt osteoporosis, to allow measures to be implemented to improve bone health (Cosman et al., 2014), thus DXA assessment may be required. Therefore, we chose to investigate if QUS could discriminate between low and normal BMD.

In this study, calcaneal QUS was significantly correlated with lumbar spine and hip BMD as measured by DXA. BUA parameter correlated with all DXA sites assessed, with correlation coefficients ranging from 0.35 (lateral spine) to 0.52 (femoral neck). SOS did not correlate with BMD at any site measured. SI correlated with spine and hip, but the association was weaker than BUA (range of 0.30 to 0.42).

QUS BUA refers to the slope between attenuation of sound signals and its frequency, measured in dB/Hz (Chin and Ima-Nirwana, 2013). Attenuation of the sound occurs because the energy is absorbed by the soft tissue and bone as the sound waves travel through them. SOS refers to the division of transmission time of the sound waves by the length of the body part studied, expressed as meter per second (m/s) (Chin and Ima-Nirwana, 2013). SI is a more sophisticated index, a

composite measure of SOS and BUA, which some researchers have suggested may be more useful in determining low bone health status (Guglielmi and de Terlizzi, 2009). SOS has been shown *in vivo* to relate closely both to BMD (Cavani et al., 2008, Cortet et al., 2004, Toyras et al., 1999) and to bone microarchitecture (Cavani et al., 2008, Cortet et al., 2004, Hans et al., 1999). Additionally, BUA has been associated with biomechanical parameters (Bouxsein and Radloff, 1997). Therefore, QUS indices appear to reflect both bone quantity (which includes BMD) and bone quality, but quantity is more important (Chin and Ima-Nirwana, 2013). In human studies, the relationship between QUS parameters and BMD is less definite: in a large study of both pre- and post-menopausal women, BUA and SOS both correlated significantly with BMD of the spine and hip (Dane et al., 2008), whereas in a study of 117 men, BUA was related to BMD, but SOS wasn't; however, SOS was able to predict fractures (Meszaros et al., 2007). A small study of 23 women with AS had significant correlation only between SOS and hip BMD (Speden et al., 2002).

In this study, QUS of the calcaneus proved to be a useful tool in identifying participants at low risk of having low BMD at any site (i.e. T-score <-1 at hip and/or spine). The BUA parameter of QUS performed best amongst all the parameters in discriminating between participants with and without low BMD, with an AUC of 0.779 for low BMD at any site. With a threshold BUA value of 117.65, a sensitivity of 93% was seen, indicating a low likelihood of missing participants with low BMD when BUA is greater than 117.65. The corresponding specificity is 55%, indicating that a number of participants with normal BMD will be classified as low BMD; however, as this is a pre-screening tool, intended to rule out individuals at low risk of low BMD, higher sensitivity is prioritised over higher specificity to minimise false negatives. The high NPV for this threshold (86%) implies that QUS could accurately out-rule individuals with low risk of low BMD.

BUA was also able to detect low BMD individually at the femoral neck and lateral spine, with thresholds giving sensitivities of 93% and 92% respectively, and NPV of 94% and 86%. QUS was unable to discriminate low BMD at the total hip or PA spine. Therefore, we conclude that using the device-specific thresholds derived in this study, QUS could be used as a pre-screening tool to accurately identify and rule-out individuals with low risk of low BMD.

Clowes et al demonstrated that by identifying a device-specific threshold in a cohort of women (pre- and post-menopausal), a diagnosis of osteoporosis could be excluded at the total hip with 95% confidence (Clowes et al., 2006). The performance of QUS at the spine was not reported in the study. Although in practice an 80% level of sensitivity and specificity is often employed, we chose to follow the ISCD guidelines of a 90% sensitivity for identifying participants who have osteoporosis (Miller et al., 2002); we did not anticipate any benefit to employing a more vigorous

threshold such as that chosen by Clowes et al (Clowes et al., 2006). In rheumatoid arthritis, QUS of the calcaneus was shown to have low ability to detect osteoporosis, but a high negative predictive value, suggesting it could have a role in screening (Cryer et al., 2007). However, a formal screening strategy has not been tested in RA, to our knowledge. In AS, Jansen et al demonstrated a high NPV in out-ruling osteoporosis using QUS (Jansen et al., 2003); however, they don't provide an explanation for their choice of T scores of <-1 and <-1.5 as QUS thresholds. The ISCD do not recommend using WHO T-score criteria with peripheral devices, as they are employing different technology to assess bone health (Miller et al., 2002); instead they recommend that device-specific cut-off points are established. Simply applying conventional DXA cut-offs in QUS measurement can underestimate the prevalence of osteoporosis (Chin and Ima-Nirwana, 2013). Our study adds to the literature by establishing device-specific cut-offs, using an adequate sensitivity, as recommended by the ISCD.

We had hoped to study the role of QUS in identifying participants at high-risk of osteoporosis. However, the prevalence of overt osteoporosis was low in this study. Therefore, we were unable to find any relationship between QUS and osteoporosis in participants and could not identify whether QUS has a role in discriminating participants at high risk of osteoporosis. This needs to be tested in an axSpA cohort with a higher prevalence of osteoporosis to make any determination about the usefulness of QUS in diagnosing osteoporosis.

Our final screening strategy was to determine whether QUS could accurately identify participants with low BMD and we found that it was not a useful tool to do this. Although thresholds were identified with high specificities (91-93%), the corresponding PPV were low (0-71%, majority between 50-60%), suggesting a low probability of actually having low BMD if the QUS reading is below the threshold value. Therefore, we conclude that in this study, QUS was not a useful tool to identify participants with low BMD.

The purpose of introducing a pre-screening or 'triage' tool is to reduce the demand on DXA, a service which is heavily oversubscribed. By introducing the 'low-risk triage approach', between 18 & 36% of DXAs could have been avoided. This has the potential to significantly ease the strain on the service. A systematic review in postmenopausal women over the age of 45 years identified that between 3% and 63% of DXAs could be avoided by introducing QUS as a pre-screen stratification tool to out-rule individuals with osteoporosis (Thomsen et al., 2015). To our knowledge, this strategy has not been previously tested in an axSpA population.

Although the purpose of this particular study was to investigate the role of QUS as a triage tool to detect low BMD, QUS of the calcaneus has been shown in different populations to also give

insight into the fragility of bone (Toyras et al., 2002, Toyras et al., 1999). QUS can provide similar, or even superior, information regarding the risk of a hip fracture when compared to BMD measured by DXA (Njeh et al., 1997). Due to the low prevalence of fragility fractures in our study, we unfortunately could not investigate this potential use of QUS. However, it is important to determine with future research if QUS has a role as an added tool to DXA in the assessment of bone health in axSpA, allowing the examination of quality, in addition to density, of bone.

6.5.1 Limitations

We would like to acknowledge some limitations to this study. As we were interested in assessing the ability of QUS to detect low BMD, we had to limit our analysis to postmenopausal women and men over the age of 50 years. Therefore, the sample size was relatively small. As a result, we may have missed additional significant relationships due to inadequate power. However, our findings advanced our knowledge regarding the utility of QUS as a pre-screening strategy in axSpA. This study should also be performed in pre-menopausal women and younger men to see if the same relationships can be seen. The prevalence of both osteoporosis and fragility fractures in this study was low, prohibiting any analysis of the role of QUS in either. A cost-effective analysis was not performed as part of this study, which would be required before QUS could be introduced as a pre-screening tool in a wider context. The thresholds established in this study are device-specific; caution is required when extrapolating the results to other devices. It is recommended that each QUS device should be validated against DXA (Chin and Ima-Nirwana, 2013) to allow bone health classification. Finally, clinical risk factors were not taken in to consideration in this study. For maximal detection of low BMD, QUS results should be interpreted in the context of the wider clinical picture.

6.6 Conclusion

In summary, this study is the first to demonstrate that QUS could be used as a triage tool to accurately identify adults with axSpA who are at low risk of low BMD and do not require onward DXA referral. Using QUS as a triage tool had the ability to avoid up to 27% of DXAs in this study. QUS was not able to confidently identify participants who had low BMD and the prevalence of osteoporosis was too low to assess its role. QUS is promising as a simple non-invasive tool to stream-line the assessment of bone health in adults with axSpA.

Chapter 7 Interventions, pharmacological and non-pharmacological for managing bone health in axial spondyloarthropathy: systematic review and meta-analysis, with recommendations

7.1 Introduction

The data presented in the preceding chapters has firmly established the high prevalence of osteoporosis in adults with axSpA. In the general population, both pharmacological and non-pharmacological interventions are effective in treating osteoporosis and are outlined in detail in Chapter 1. In RA, TNF-inhibitors have been shown to preserve or improve spine and hip BMD in a systematic review (Zerbini et al., 2017). Denosumab increased BMD at the hip and spine over 24 months in a small retrospective study of individuals with RA (Nakamura et al., 2017). Bisphosphonates were effective in maintaining BMD in RA (Tada et al., 2017), although persistence with bisphosphonate therapy was shown to be low (33%) three years into treatment in a real-life setting (Park et al., 2017).

The treatment of osteoporosis was deemed outside the scope of the 2016 ASAS-EULAR management recommendations for axSpA (van der Heijde et al., 2017) and so currently clinicians treating patients with axSpA have no clear guidelines to follow when considering the treatment of osteoporosis. An effective means of treating low BMD in individuals with axSpA is needed. Therefore, there is a need to synthesise the evidence regarding treatment of low BMD in individuals with axSpA.

7.2 Aims

The purpose of undertaking this review was to synthesise the effect of treatment on BMD in individuals with axSpA, based on evidence from randomised-controlled trials (RCTs) and quasi-RCTs (qRCTs). We aimed to systematically review the effect of both non-pharmacological and pharmacological interventions on BMD.

7.2.1 Specific objectives

1. Assess the effect of osteoporosis medication on BMD of hip and spine in axSpA
2. Assess the impact of disease-specific treatment (conventional and biological DMARDs) on BMD in axSpA
3. Assess the impact of non-pharmacological interventions on BMD in axSpA.

7.3 Methods

7.3.1 Protocol and registration

This systematic review is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Liberati et al., 2009). Prior to commencing the review, the study protocol was prospectively registered online with a registry of systematic reviews (available at https://www.crd.york.ac.uk/prospero/; ID CRD42018104559; see Appendix B).

7.3.2 Study eligibility criteria

The review included studies with participants aged 18 or over and with a diagnosis of axSpA according to the 2009 ASAS criteria or AS according to mNY criteria. There were no restrictions on gender.

Studies were eligible for inclusion in the review if they included pharmacological and/or non-pharmacological interventions. All medications specifically prescribed to improve BMD were eligible for inclusion. In addition, all disease-modifying anti-rheumatic medications (conventional and biologic) were eligible, if the other eligibility criteria were satisfied. Interventions consisting of general advice to improve bone health without specific pharmacological or non-pharmacological intervention were not eligible. We included interventions which were compared to no intervention, placebo, standard care or other specified intervention. There were no restrictions on the setting of the intervention (i.e. hospital-based, community-based, online interventions).

The outcome of interest was BMD. The outcome could be assessed at the lumbar spine, and/or hip. BMD measurements at other sites were not included. Studies were eligible if BMD was objectively measured by DXA or qCT. BMD had to be measured at a minimum of two separate

time points. Studies which included BMD as the sole target of the intervention were included. In addition, studies in which BMD was not the target of the intervention were included, provided BMD was measured pre- and post-intervention and all other eligibility criteria were met. Studies of all duration were eligible.

Randomised controlled trials (RCTs) and quasi-randomised controlled trials (qRCTs, participants are allocated to different arms in a method of allocation that is not truly random) were included. The following study designs were excluded: observational studies without control groups, case-control studies, case reports, cross-sectional studies, commentaries, expert opinion and review articles.

7.3.3 Search methods for identification of studies

To retrieve studies, electronic databases were searched from inception to June 2019. No search restrictions were imposed. Databases searched were EMBASE, Medline (OVID), CINAHL, Cochrane library (CENTRAL) and Web of Science. Search terms used were adapted as appropriate for each database and are summarised in Appendix F. The search strategy was performed by an experienced librarian. In the case of an abstract only being available, the author(s) was contacted to request a full-text. The electronic database search was augmented by a hand-search of the reference list of included articles.

Two reviewers independently screened the titles and abstracts of all studies to identify those that potentially met the eligibility criteria. Full-texts of potentially relevant articles were obtained and screened by two independent reviewers. Any disagreements between the two reviewers on the eligibility of an article were resolved by discussion to reach a consensus, or referral to a third reviewer if required. Covidence software was used to assist the selection of studies (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org).

Data extraction was performed by GF. A customised electronic data extraction form was used. Details regarding study characteristics, participants, intervention and study outcomes were collected. Authors were contacted as required to request further information or clarification on published data.

7.3.4 Assessment of risk of bias in included studies

An assessment of the risk of bias in the included studies was independently performed by two reviewers. Any disagreements between the reviewers were resolved through discussion, and if necessary, by consulting a third reviewer, to achieve consensus. The revised Cochrane risk-of-bias tool for randomised trials (RoB2) was used (Higgins et al., 2016). Each included study was accordingly judged as having a low or high risk of bias, or as some concerns of risk of bias, across five domains (bias arising from randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, bias in selection of the reported result). Information used to make this judgement was primarily based on the published manuscript. However, additional information was also used if available e.g. published protocols.

7.3.5 Quality of evidence

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was used to assess the quality of evidence for each outcome (Schunemann et al., 2011). Quality ratings could be high, moderate, low or very low, with only RCTs being assigned the highest grade. Evidence could be downgraded if there were limitations in the design and implementation of studies suggesting a high likelihood of bias, indirectness of evidence, inconsistency of results and/or imprecision. The GRADE approach was also used to determine the strength and direction of recommendations (Andrews et al., 2013a, Andrews et al., 2013b).

7.3.6 Measures of treatment effect

The mean difference in the BMD between the control and intervention group at the study end-point, along with 95% confidence intervals, was calculated. When available, the mean final value score was extracted. If not available, the change-from-baseline score was instead extracted. If different units of measurement were used (e.g BMD can be measured in g/cm^2, T scores or Z scores), standardised mean difference (SMD) was used (2011). If the outcome was measured at several time-points, data was extracted at the final time-point reported.

7.3.7 Data synthesis

When appropriate, results of trials with comparable results were pooled. Studies were pooled according to the intervention administered and the site where BMD was assessed. In this situation, a random-effects model was used. The extent of heterogeneity was used to guide the decision to pool studies. Clinical heterogeneity was assessed subjectively; the assessment was based on the participants of the study, the intervention administered, and the outcomes measured. Statistical heterogeneity was assessed using a combination of the I^2 statistic, where ≥75% indicates significant heterogeneity (2011), and the p-value of the Chi-square test, with a p-value of <0.01 indicating significant heterogeneity. If studies were not pooled due to significant heterogeneity, results were presented in tables and synthesised qualitatively.

7.4 Results

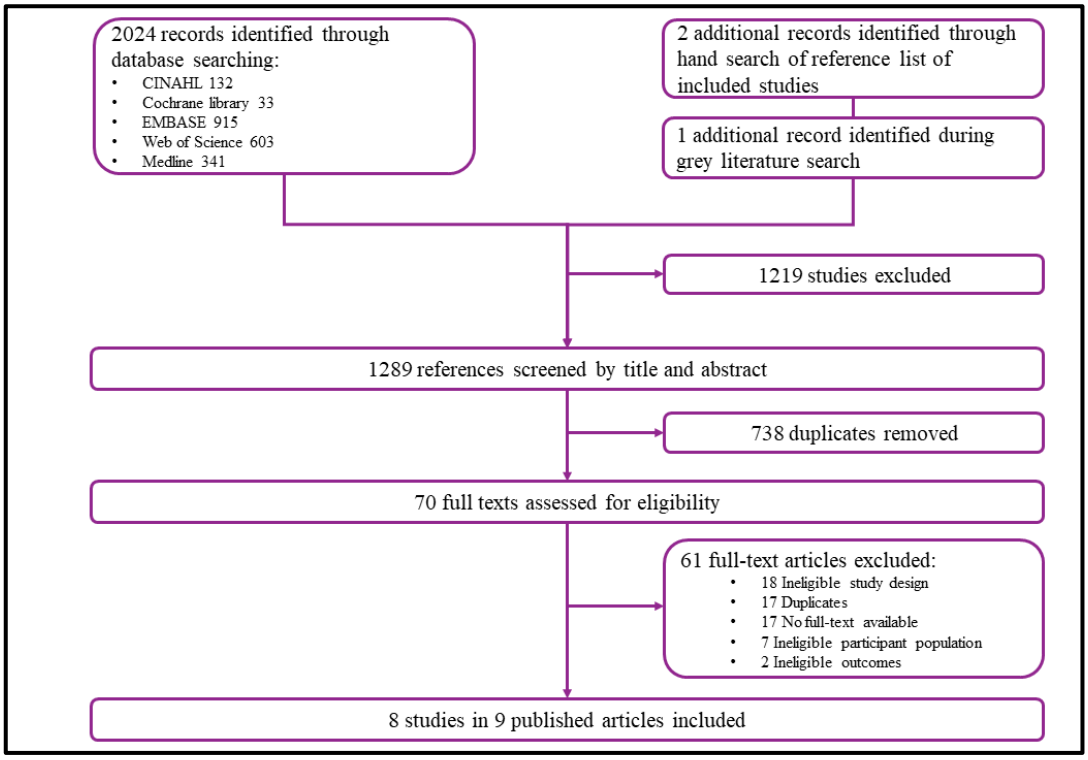
7.4.1 Study selection

The study screening and selection process is outlined in detail in Figure 7-1. The initial study screening process consisted of 1289 records, after removing duplicates. Studies were excluded for the following reasons: ineligible study design, duplicates, no full-text available, ineligible participant population, ineligible outcome measures. If a full-text manuscript contained information in a format that was unsuitable for use or had omissions of data, authors were contacted to request clarification or further information.

The methods section of one reviewed paper outlined that BMD data was collected but reported in a separate manuscript (Coates et al., 2017). The authors of the study were contacted and provided us with a text of the manuscript reporting the BMD data (Creamer et al., 2017). The results of the two studies were pooled under Creamer et al. (Creamer et al., 2017), as this paper specifically reported the BMD data, supplemented as required with additional information regarding the study population from the original paper (Coates et al., 2017).

Following this process, a total of eight studies, with results reported across nine articles (Coates et al., 2017, Viapiana et al., 2014, Soroush et al., 2016, Li et al., 2015, Marzo-Ortega et al., 2005, Mihailov et al., 2015, Khabbazi et al., 2014, Kang et al., 2013, Creamer et al., 2017), met the eligibility criteria and were included in the review. All included studies were published in English.

Figure 7-1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram outlining the study selection process.



7.4.2 Study characteristics

7.4.2.1 Design and participants

Study characteristics are outlined in Table 7-1. Two of the included studies were RCTs (Creamer et al., 2017, Marzo-Ortega et al., 2005) and five were qRCTs (Mihailov et al., 2015, Viapiana et al., 2014, Li et al., 2015, Kang et al., 2013, Soroush et al., 2016, Khabbazi et al., 2014). The eighth study by Soroush et al described itself as a cross-sectional study (Soroush et al., 2016), but on screening the article, the authors made the decision to include the study and classify as a qRCT, as participants were assigned to two different groups and followed prospectively, fulfilling the inclusion criteria for this review. Three of the included studies assessed the efficacy of the oral bisphosphonate alendronate (Creamer et al., 2017, Khabbazi et al., 2014, Soroush et al., 2016) and three assessed the effect of TNF-inhibitors (Kang et al., 2013, Li et al., 2015, Marzo-Ortega et al., 2005) on BMD. Mihailov et al (Mihailov et al., 2015) divided patients into three groups (NSAIDs, sulfasalazine and biological treatment) and administered peloidotherapy to 56-69% of each group. Viapiana et al compared the effect on BMD of an intravenous bisphosphonate (neridronate) to infliximab (Viapiana et al., 2014).

In the alendronate intervention studies, the duration of the intervention ranged from 12 months (Khabbazi et al., 2014, Soroush et al., 2016) to 24 months (Creamer et al., 2017). In the tumour necrosis factor-inhibitor (TNFi) trials, the shortest duration was 30 weeks (Marzo-Ortega et al., 2005) and the longest was 24 months (Kang et al., 2013). The peloidotherapy intervention was six months in duration (Mihailov et al., 2015), as was the trial comparing a bisphosphonate to TNFi (Viapiana et al., 2014).

The total number of participants was 602. There was a male majority in all studies, ranging from 54% (Khabbazi et al., 2014) to 92% (Kang et al., 2013). The studies included participants from the UK (Marzo-Ortega et al., 2005, Creamer et al., 2017), South Korea (Kang et al., 2013), Iran (Soroush et al., 2016, Khabbazi et al., 2014), China (Li et al., 2015), Romania (Mihailov et al., 2015) and Italy (Viapiana et al., 2014). Baseline demographics were not reported in one study (Mihailov et al., 2015). Detailed information of participant characteristics is outlined in Table 7-2.

7.4.2.2 Outcome measures

Bone mineral density was the primary outcome in four studies (Kang et al., 2013, Li et al., 2015, Soroush et al., 2016, Khabbazi et al., 2014). Although our protocol allowed for BMD measured by DXA or qCT, no studies using qCT fulfilling the eligibility criteria were identified. All studies used DXA (different machines used, see Table 7-1) to assess BMD. BMD was assessed in all eight studies at the lumbar spine, at the femoral neck in six studies (Soroush et al., 2016, Mihailov et al., 2015, Marzo-Ortega et al., 2005, Li et al., 2015, Kang et al., 2013, Creamer et al., 2017), total hip in three studies (Marzo-Ortega et al., 2005, Kang et al., 2013, Creamer et al., 2017) and unspecified hip site in two studies (Khabbazi et al., 2014, Viapiana et al., 2014). The authors were contacted to clarify the hip site, but a response is pending.

Table 7-1: Summary of setting and design of included studies.

Study	Location	Study design	Duration†	BMD assessment method (sites) Make of DXA machine	Inclusion/exclusion criteria
Alendronate trials					
(Creamer et al., 2017)	6 centres, UK	RCT	24m	DXA (spine, femoral neck, trochanteric, total hip) Hologic x 4 centres GE Lunar x 2 centres	***Inclusion*:** refined mNY criteria (allowed sacroiliitis on MRI + minimum pre-defined movement restriction), ASAS criteria, age>21 years, stable dose of NSAID x 4/52. ***Exclusion* :** oesophageal/peptic ulceration, abnormalities of bone turnover and calcium metabolism, bisphosphonates in previous12 months, oral or IV steroid within 3 months, IA steroids within 2 months, TNF-alpha therapy, calcitonin, raloxifene, testosterone, HRT change within 6 months, ≥2 minimal trauma fractures, allergy to bisphosphonates, significant renal disease, lumbar spinal surgery, bilateral hip replacements, planned surgery within study period, pharmaceutical trials, pregnancy (current or planning), malignancy, life expectancy ≤2 years.
(Khabbazi et al., 2014)	Tabriz, Iran	qRCT	12m	DXA (spine & hip [site not specified]) Hologic QDR	***Inclusion*:** referred to outpatient clinic, fulfil ASAS criteria, early stage of AS (Schober's ≥5, normal hip joint in pelvic x-ray, Taylor index ≤1, T-score ≤-1.5. ***Exclusion*:** previous history of spinal fracture, bisphosphonate use, steroid use, pregnancy, lactation, hypothyroidism, hyperparathyroidism, osteomalacia, hyperparathyroidism, diabetes mellitus, liver failure, kidney failure

Study	Location	Study design	Duration†	BMD assessment method (sites) Make of DXA machine	Inclusion/exclusion criteria
(Soroush et al., 2016) [a]	Tehran, Iran	qRCT	12m	Bone densitometry (spine, femoral neck) NR	***Inclusion*:** reviewed by Rheumatology Specialist, AS by mNY criteria ***Exclusion*:** NR
TNF inhibitor trials					
(Kang et al., 2013)	Seoul, South Korea	qRCT	24m	DXA (spine (L1-L4) and hip (femoral neck & total proximal femur)) Lumbar Prodigy densitometer	*Inclusion*: mNY criteria, followed up at rheumatology department *Exclusion*: other forms of SpA, history of neuroendocrine disorders, chronic renal disease, excessive alcohol intake
(Li et al., 2015)	Guangzhou, China	qRCT	12m	DXA (spine (L2-L4) & femoral neck) Medlink	*Inclusion*: visited dept of rheumatology, fulfil mNY criteria, BASDAI > 4, low BMD (Z score < 1) *Exclusion*: previous/current antiosteoporotic treatment, history of fracture, glucocorticoids or anti-TNF therapy in last 3 months, history of alcohol dependence, type 2 diabetes, thyroid disease, parathyroid disease, tuberculosis, postmenopausal women, pregnant women.
(Marzo-Ortega et al., 2005)	Yorkshire, UK	RCT	30w	DXA of spine (L2-L4), femoral neck and total hip Lunar Expert	*Inclusion*: recruited from specialist rheumatology clinics, fulfil mNY criteria, >18 years old, active spinal disease defined as persistent IBP (VAS ≥3cm and CRP >10mg/l despite tx with NSAIDs or DMARDs). *Exclusion*: history of TB, active infection, demyelinating disease, previous lymphoproliferative or malignant disorder, pregnancy, breastfeeding, uncontrolled concomitant disease in opinion of investigator, received investigational drug within 3/12 of start of study

Study	Location	Study design	Duration[†]	BMD assessment method (sites) Make of DXA machine	Inclusion/exclusion criteria
Bisphosphonate versus TNFi					
(Viapiana et al., 2014)	Verona, Italy	qRCT	6m	DXA (lumbar spine & hip) Hologic	*Inclusion*: fulfil mNY criteria, BASDAI ≥4, stable dose x 3 months if taking SSZ *Exclusion*: steroid therapy within 3 months, renal insufficiency (creatinine ≥2 mg/dl), severe infections, history of TB, HBV, HCV, neuropathy or malignancy within past 5 years
Non-pharmacological intervention					
(Mihailov et al., 2015)	Constanta, Romania	qRCT	6m	DXA of spine (L2-L4) and femoral neck Lunar General Electric	*Inclusion*: fulfil mNY criteria, back pain during 3 months prior to enrolment *Exclusion*: psoriasis, seronegative SpA (other than AS), malignancies, equilibrium disturbance, mental disorders, other active non-inflammatory disease

[†] *m: months; w: weeks.*

[a] *Study self-describes as cross-sectional; however methods describe pre- and post-intervention BMD measurement and other inclusion criteria met, hence decision to include and label as qRCT.*

AS: ankylosing spondylitis; ASAS: Assessment of SpondyloArthritis Society; BASDAI: Bath AS disease activity index; BMD: bone mineral density; CRP: C-reactive protein; DMARDs: disease-modifying anti-rheumatic drugs; DXA: dual-energy x-ray absorptiometry; GE: General Electric company; HBV: hepatitis B virus; HCV: hepatitis C virus; HRT: hormone-replacement therapy; IA: intra-articular; IBP: inflammatory back pain; mNY: modified New York; MRI: magnetic resonance imaging; NR: not-reported; NSAIDs: non-steroidal anti-inflammatory drugs; QDR: quantitative digital radiography; qRCT: quasi-randomised controlled trial; RCT: randomised controlled trial; SpA: spondyloarthropathy; SSZ: sulphasalazine; TB: tuberculosis; TNFi: tumour-necrosis factor inhibitor; tx: treatment; UK: United Kingdom; VAS: visual analogue scale;

7.4.3 Intervention

7.4.3.1 Pharmacological interventions

Oral bisphosphonates

Detailed information regarding all interventions is outlined in Table 7-2. The effect of alendronate, an oral bisphosphonate, was the intervention assessed in three studies (Creamer et al., 2017, Khabbazi et al., 2014, Soroush et al., 2016). In two of these studies, the effect of alendronate was compared to placebo (Khabbazi et al., 2014, Creamer et al., 2017). The third study compared alendronate to no treatment (Soroush et al., 2016); however, both groups received 'standard treatment': details regarding what the standard treatment included were not provided in the manuscript; the authors were contacted to clarify, but no further information is available at the time of submission of this manuscript. In addition, 14 of the 29 individuals in this study assigned to alendronate received glucocorticoids. Table four in the manuscript reports the BMD results for the individuals who received steroids separately to those who received alendronate alone, but the post-treatment BMD figure for the alendronate-only group is blank and no response has been received from the authors when contacted by e-mail to clarify. Therefore, it was not suitable to pool this alendronate study with the other two, and so is reported qualitatively only. Adherence was assessed in Creamer et al by recording tablet counts, with all individuals taking at least 70% of prescribed medication (Creamer et al., 2017). Adherence information was not reported in the remaining two manuscripts.

TNF inhibitors

The effect of TNFi on BMD was the intervention assessed in three studies (Kang et al., 2013, Li et al., 2015, Marzo-Ortega et al., 2005). One study was placebo-controlled; both arms were additionally prescribed methotrexate and infliximab was the TNFi of choice (Marzo-Ortega et al., 2005). The remaining two studies compared the TNFi to oral DMARDs: SSZ alone (Li et al., 2015) or choice of SSZ or MTX (Kang et al., 2013). A combination of TNFi were used in these two studies: etanercept and adalimumab were used in both studies, and infliximab was additionally used in Kang et al (Kang et al., 2013). In the studies with combinations of TNFi, the BMD outcomes were not reported for each individual TNFi, therefore subgroup analysis of individual TNFi was not possible. In all three studies, NSAIDs were allowed, on demand (Kang et al., 2013) or on a stable unchanged dose (Marzo-Ortega et al., 2005). In Li et al (Li et al., 2015), NSAIDs could be taken within twelve weeks of the study, with significantly higher use in the control group at baseline, but no details on NSAID use during the trial were given. No information on adherence to the intervention was reported in any of the three manuscripts. However, the placebo-controlled trial (Marzo-Ortega et al., 2005) required intravenous infusions administered

in a hospital setting, therefore adherence can be assumed for all participants that completed the trial.

Bisphosphonate versus TNFi

One study compared the effect of an IV bisphosphonate called neridronate with a TNFi (specifically infliximab) (Viapiana et al., 2014). Stable doses of SSZ were allowed in both arms. No information on adherence to the intervention was reported in the manuscript.

7.4.3.2 Non-pharmacological interventions

Only one study which presented itself as assessing a non-pharmacological intervention was identified: the efficacy of peloidotherapy from the Techirghiol lake in Romania on patients with AS (Mihailov et al., 2015). The peloidotherapy treatment is described in the manuscripts as application of a warm mud pack for 20 minutes, followed by 20 minutes bathing in either a heated swimming pool or salted mineral water of the lake, which was also warm. Eighty-seven patients were divided into three groups: treatment with NSAIDs (n=25), SSZ (n=27) or biological treatment (n=35). A proportion of each group (56-69%) were treated with peloidotherapy. However, the results reported in the manuscripts were only for the proportion of the groups who had received the peloidotherapy; therefore, in reality this study reported the results of three groups comparing NSAIDs to SSZ to biological treatment. No details on what the biological treatment entailed were included in the report. The authors of the paper were contacted in an attempt to clarify, but at the time of submission, no further information is available.

Table 7-2: Summary of participant and intervention characteristics.

Study	Group	Participant baseline characteristics[a]						Intervention		
		Age, yrs	*Male*	*Disease duration, yrs*	*BASDAI*	*HLA-B27+*	*Medication use*	*Description*	*Duration[§]*	*Adherence*
(Creamer et al., 2017)	Bisphosphonate *N=88*	47.1 (11.6)	74 (84)	19.7 (10.7)	4.2 (2.4)	NR	NSAIDs 84 (95.5)	Alendronate 70mg weekly	24m	Tablet counts recorded All patients complied with protocol requirement of at least 70% of study medication
	Control *N=92*	47.4 (12.3)	74 (80)	20.8 (12.7)	4.1 (2.1)	NR	NSAIDs 74 (80.4)	Placebo (matching tablets)		
(Khabbazi et al., 2014)	Bisphosphonate *N=11*	33.4 (7.8)	7 (64)	5.18 (4.5)	7.34 (2.6)	9 (82)	NSAIDs[†]	Alendronate 70mg weekly + calcium 1000mg od + vitamin D 300mg od	12m	NR
	Control *N=13*	32.9 (7.6)	7 (54)	5.5 (4.8)	7.18 (2.4)	12 (92)	NSAIDs[†]	Placebo + Calcium 1000mg od + vitamin D 400mg od		
(Soroush et al., 2016)	Bisphosphonate *N=29*	10.8 (35.9)	49 (86)	NR	NR	34 (60)	48% of alendronate group received glucocorticoids	Alendronate 70mg weekly + standard treatment	12m	NR
	Control *N=28*	*Not reported separately, figures above apply to whole group*						Standard treatment		
(Kang et al., 2013)	TNFi *N=26*	36.5 (10.3)	24 (92)	9.5 (5.1)	NR	19 (83)	Bisphosphonates 12 (46.2) + NSAIDs prn[†]	TNF-i + NSAIDs Infliximab 5 (19) Etanercept 18 (69) Adalimumab 3 (12)	24m	NR
	Control *N=37*	38.6 (10.3)	28 (76)	8.0 (4.5)	NR	28 (90)	Bisphosphonates 17 (45.9) + NSAIDs prn +/- MTX +/- SSZ[†]	NSAIDs +/- MTX +/- SSZ		

Study	Group	Participant baseline characteristics[a]						Intervention		
		Age, yrs	*Male*	*Disease duration, yrs*	*BASDAI*	*HLA-B27+*	*Medication use*	*Description*	*Duration[§]*	*Adherence*
(Li et al., 2015)	TNFi *N=42*	39.6 (7.5)	37 (88)	16.4 (4.8)	5.84 (1.8)	40 (95)	NSAIDs 14 (33)	Etanercept 50mg/week (n=25) or adalimumab 40mg/fortnight (n=17) + calcium 1.0 g/day + vitamin D 800-1000 IU/day	52w	NR
	Control *N=47*	41.9 (8.7)	40 (85)	17.5 (5.9)	5.06 (1.27)	43 (91)	NSAIDs 28 (59)	Sulfasalazine 1g bd + calcium 1000mg od + vitamin D 800-1000 IU/day		
(Marzo-Ortega et al., 2005)	TNFi *N=23 (hip)/24 (spine)*	41 (28-74)	23 (82)	8 (0-41)	6.9 (2.11-9.26)	96%	NSAIDs 25 (89), oral steroids 5 (18), DMARDs 10 (36)	Infliximab (week 0, 2, 6, 14, 22) + MTX (7.5mg to be eventually increased to 10mg weekly)	30w	Treatment administered in outpatient facility; all patients completed study; full adherence presumed
	Control *N=8 (hip)/10 (spine)*	39 (30-56)	11 (76)	10 (0-35)	6.4 (3-10)	86%	NSAIDs 12 (86), oral steroids 3 (25), DMARDs 4 (21)	Placebo + MTX (7.5mg to be eventually increased to 10mg weekly)		
(Viapiana et al., 2014)	Bisphosphonate *N=30*	49.4 (15.0)	21 (70)	142m (145)	5.24 (1.60)	95%	NSAIDs prn + SSZ 1	Neridronate 100mg IV monthly x 6/12	6m	Intravenous infusion administered; 93% completed IFX leg, 64% completed placebo leg
	TNFi *N=30*	43.1 (12.2)	20 (67)	129m (107)	4.86 (1.17)	95%	NSAIDs prn + SSZ 1	Infliximab 5mg/kg at week 0, 2 and 4, then every 6 weeks x 6/12 total		
(Mihailov et al., 2015)	Gp1:16 Gp2: 15 Gp3: 24	NR	NR	NR	NR	NR	NR	Gp1: NSAID + peloidotherapy Gp2: SSZ + peloidotherapy Gp3: Biological tx + peloidotherapy	6m	NR
	Gp 1:9 Gp2: 12 Gp3: 11	NR	NR	NR	NR	NR	NR	Gp1: NSAID Gp2: SSZ Gp3: biological tx		

[a] *Expressed as mean (SD) or n (%) or median (range), unless otherwise stated.*

[†] *Prevalence of usage not reported*

[§] *m: months; w: weeks.*

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; bd: "bis in die" (twice daily); DMARDs: disease-modifying anti-rheumatic drugs; Gp: group; HLA-B27+: human leucocyte antigen B27 positive; IFX: infliximab; IU: international units; IV: intravenous; MTX: methotrexate; NR: not reported; NSAID: non-steroidal anti-inflammatory drug; od: "omne in die" (once daily); prn: "pro re nata" (as needed); SSZ: sulphasalazine; TNFi: tumour necrosis factor-inhibitors; tx: treatment;

7.4.4 Risk of bias in included studies

The risk of bias of the eight included studies is summarised by domain in Figure 7-2 and by study in Figure 7-3. Studies often included an assessment of "some concerns" with regards to risk of bias, largely due to a lack of information in the study which was unable to be clarified by attempts to contact authors. In total, only one study was deemed to have an overall high risk of bias (Mihailov et al., 2015) and one to have a low risk of overall bias (Khabbazi et al., 2014), with the remaining judged to have "some concerns" for overall bias.

7.4.4.1 Bias arising from randomisation process

Three studies were judged as high risk in this domain. Kang et al (Kang et al., 2013) allocated treatment based on the 'discretion of the attending rheumatologist', therefore the allocation sequence was not concealed; no details were provided on a randomisation process in Li et al (Li et al., 2015), other than patients were 'randomly divided', with the choice of TNF blocker based on 'the judgement of the rheumatologist', suggesting the allocation wasn't concealed; Mihailov et al (Mihailov et al., 2015) stated that patients were 'randomly allocated by a coordinator study nurse', without any details of the process and there were significant baseline differences between the groups, suggesting an ineffective randomisation process.

Two studies were deemed to be low risk as the allocation sequence was concealed and random, with no differences between baseline characteristics to suggest an issue with the process (Khabbazi et al., 2014, Marzo-Ortega et al., 2005). The remaining three studies were deemed to have "some concerns" for bias arising from the randomisation process.

7.4.4.2 Bias due to deviations from intended interventions

One study was judged as high risk in this domain (Soroush et al., 2016) as there was no information provided on whether blinding was in effect, whether there was any deviation from the intended intervention or whether an appropriate analysis was used to estimate the effect of assignment to intervention. Two studies were judged as low risk of bias (Khabbazi et al., 2014, Marzo-Ortega et al., 2005) as participants were blinded to the intervention groups and appropriate analyses were performed to analyse efficacy. Creamer et al (Creamer et al., 2017) was deemed to have some concerns, as the number of patients analysed in each group was not reported, therefore although the methods section states analysis was performed on an "intention to treat" principle, this couldn't be verified. Kang et al (Kang et al., 2013) was judged to have some concerns in this domain, as participants and assessors were aware of the intervention and there was no information on any deviations from intended intervention. In three studies (Li et al., 2015, Viapiana et al., 2014, Mihailov et al., 2015), there is no information on whether those who performed the

assessments were blinded to the assigned intervention, therefore there were some concerns regarding risk of bias for this domain.

7.4.4.3 Bias due to missing outcome data

Four studies were deemed at high risk of bias in this domain (Creamer et al., 2017, Li et al., 2015, Marzo-Ortega et al., 2005, Mihailov et al., 2015). In Creamer et al (Creamer et al., 2017), the missing outcome data is presented in relation to a different study looking at the clinical efficacy of alendronate (Coates et al., 2017). It is not clear if the same numbers apply to the BMD data, therefore there is a high risk of bias. Two studies (Li et al., 2015, Marzo-Ortega et al., 2005) did not have data available for all randomised participants, with larger numbers dropping out of the control groups due to inefficacy of treatment, representing a high risk of bias as the reason for drop out may relate to the true value of the missing outcome. In Mihailov et al (Mihailov et al., 2015), results were only reported for a subgroup of patients, with no information provided on why that decision was made. Studies were deemed at low risk if there was no or very little missing outcome data (Viapiana et al., 2014, Kang et al., 2013, Khabbazi et al., 2014). One study was judged as having some concerns with regards to bias, as insufficient information was provided to adequately assess the risk (Soroush et al., 2016).

7.4.4.4 Bias in the measurement of outcome

No studies were assessed as high risk of bias in this domain. Studies were assessed as low risk if the method of measuring the outcome was appropriate, the measurement did not differ between groups and outcome assessors were either blinded or it was deemed that knowledge of the intervention assignment would not influence the assessment of BMD (Viapiana et al., 2014, Li et al., 2015, Khabbazi et al., 2014, Creamer et al., 2017, Marzo-Ortega et al., 2005). Three studies were deemed to have some concerns, due to insufficient information allowing an accurate assessment, but no indications of high risk (Kang et al., 2013, Soroush et al., 2016, Mihailov et al., 2015).

7.4.4.5 Bias in selection of the reported result

Only one study was judged low risk of bias in this domain (Khabbazi et al., 2014), as it fulfilled all elements of the pre-published protocol. The remaining studies were deemed to have some concerns, as it was not possible to judge if there had been bias in selection of the reported results.

Figure 7-2: Risk of bias by study. Review authors' judgements about each risk of bias item for each included study.

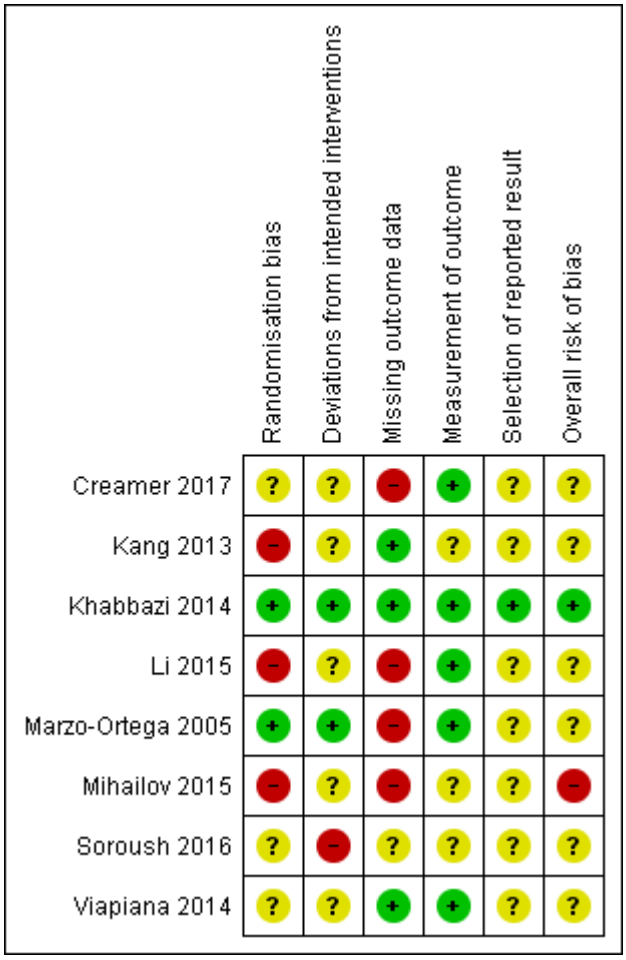
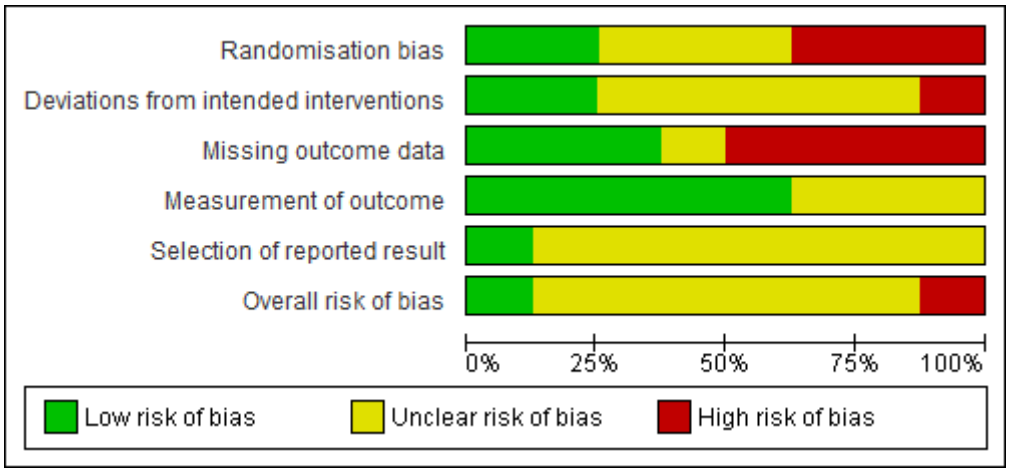


Figure 7-3: Risk of bias by domain. Review authors' judgements about each risk of bias item presented as percentages across all included studies.



7.4.5 Effects of interventions

Intervention effects are reported according to the intervention used and its effect on each outcome measured. Meta-analysis was planned if there were sufficient studies to pool, without significant heterogeneity. However, there was significant heterogeneity with respect to interventions and outcome measures, thus limiting meta-analysis of the included studies. The effects of the interventions are summarised in Table 7-3.

7.4.5.1 Comparison 1: Alendronate versus placebo or standard treatment

Two studies examined the effect of alendronate compared to placebo (Creamer et al., 2017, Khabbazi et al., 2014) reporting data on 204 participants in total. One of these studies was considered at low risk of bias (Khabbazi et al., 2014) and the other as having some concerns (Creamer et al., 2017).

Both studies (Creamer et al., 2017, Khabbazi et al., 2014) investigated the effect of alendronate on BMD at the *lumbar spine* and the studies were not suitable for pooling due to substantial heterogeneity (I^2=98%, see Figure 7-4). Khabbazi et al (Khabbazi et al., 2014) found no effect on BMD of the lumbar spine after twelve months. Creamer et al (Creamer et al., 2017) found a significant effect on the percentage change of BMD at the lumbar spine favouring alendronate (MD 4.22, 95% CI 2.93 to 5.51; Figure 7-4). The strength of evidence for this outcome was low, downgraded due to imprecision and a high likelihood of the qRCT study design (Khabbazi et al., 2014) introducing bias.

Creamer et al (Creamer et al., 2017) was the only study to assess the effect of alendronate at the *femoral neck* and found a significant effect favouring alendronate (MD 2.01, 95% CI 0.67 to 3.35; Figure 4). Strength of evidence was moderate, downgraded due to imprecision.

Both studies (Creamer et al., 2017, Khabbazi et al., 2014) investigated the effect of alendronate on BMD of the *total hip*, again with significant heterogeneity prohibiting pooling of the studies (I^2=97%). Creamer et al (Creamer et al., 2017) demonstrated a significant effect favouring alendronate (MD of 2.98, 95% CI 2.05 to 3.91; Figure 7-4) on BMD. Khabbazi et al found no effect on BMD of the total hip (MD 0.05, 95% CI -0.06 to 0.16). Strength of evidence for this outcome was low, downgraded due to imprecision and risk of bias from the study design.

Creamer et al (Creamer et al., 2017) assessed the effect of alendronate at *intertrochanteric hip* and found a significant effect favouring alendronate (MD 3.7, 95% CI 2.49 to 4.91; Figure 7-4), with a moderate strength of evidence for this outcome, downgraded due to imprecision.

Soroush et al (Soroush et al., 2016) compared the effect of alendronate to no treatment in 57 participants, with half the intervention group receiving glucocorticoids. In this study (see Figure 7-5), authors examined the effect of alendronate on BMD at the lumbar spine and femoral neck, with no significant effect on BMD at the lumbar spine and a significant effect favouring 'standard treatment' at the femoral neck (MD -1.74, 95% CI -2.33 to -1.15). However, patients with glucocorticoids were included in the intervention arm, accounting for 51% of the population. One table (Table 4 in the paper) presented the results at femoral neck of patients with and without alendronate separately, but the post-treatment figure for the alendronate-only group was omitted from the table. The authors were contacted to request the data for the patients without exposure to glucocorticoids, but this was not available at the time of submission. Therefore, the effect of glucocorticoids could not be accounted for. In addition, there was significant differences in baseline T-scores between the two groups. The strength of evidence for both outcomes in this study is very low. The grade was downgraded twice due to limitations in the design of the study, in particular with randomisation, evident from the significant baseline differences between the control and intervention group, and with the paucity of data on the effect of glucocorticoids. It was downgraded a further step due to imprecision, with small numbers in both arms.

In summary, there was low strength of evidence showing no effect of alendronate on BMD of the lumbar spine. In addition, there was moderate strength of evidence showing an effect favouring alendronate on femoral neck and intertrochanteric hip BMD, but low strength of evidence showing no effect on total hip BMD. The effect of alendronate with steroids on lumbar spine and femoral neck BMD cannot be assessed due to very low strength of evidence for these outcomes. Overall the current balance of evidence supports a conditional recommendation for alendronate over placebo in treating BMD of the hip, but no recommendation for the spine.

Figure 7-4: Forest plots demonstrating effect of alendronate on outcomes (lumbar spine, femoral neck, total hip, intertrochanteric hip).

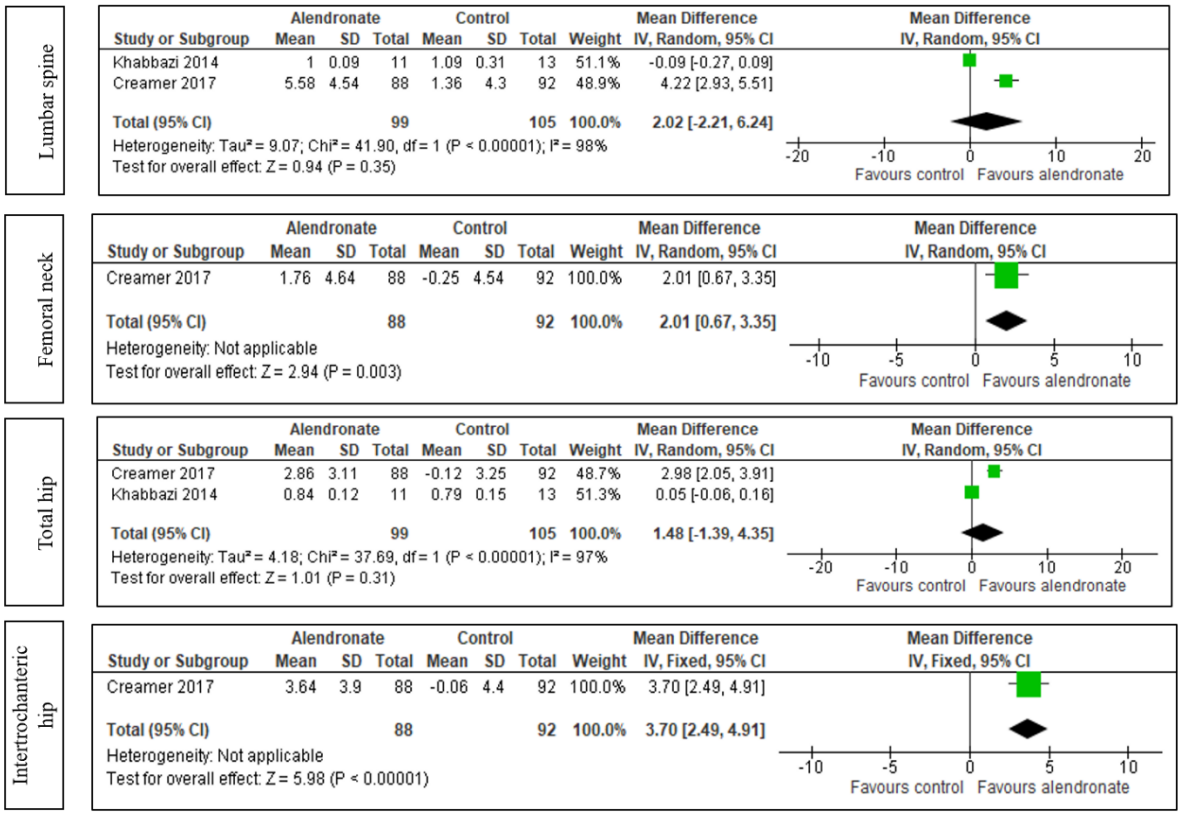
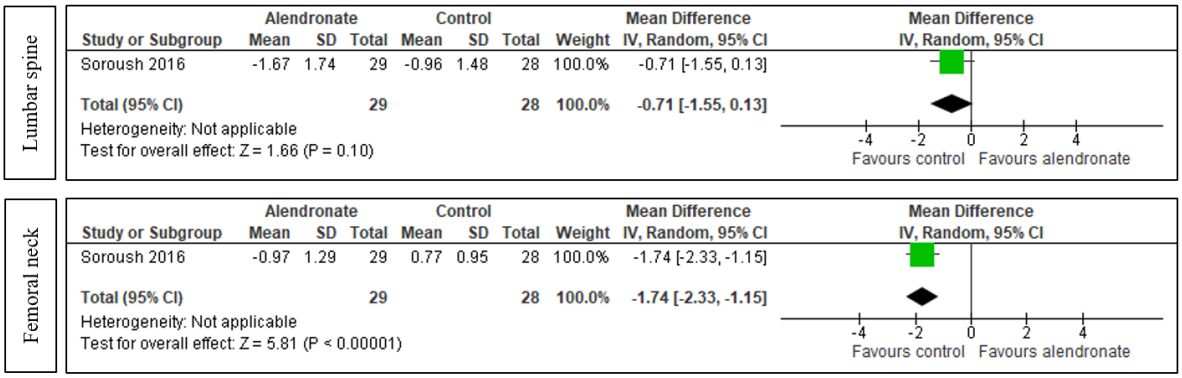


Figure 7-5: Forest plots demonstrating effect of alendronate in combination with steroids on outcomes (lumbar spine, femoral neck).



7.4.5.2 Comparison 2: TNFi versus placebo or standard treatment

Three studies investigated the effect of TNFi on BMD, reporting data on 194 participants (Kang et al., 2013, Li et al., 2015, Marzo-Ortega et al., 2005). All the studies were judged as having some concerns with regards to the risk of bias.

The three studies investigated the efficacy of TNFi on BMD of the *lumbar spine*. Studies were not pooled due to heterogeneity (I^2=90%; Figure 7-6). Marzo-Ortega et al (Marzo-Ortega et al., 2005) and Kang et al (Kang et al., 2013) found no significant effect of TNFi on BMD. In contrast, Li et al (Li et al., 2015) found a significant effect favouring TNFi over SSZ (MD 23.5%, 95% CI 17.77 to 29.23; Figure 7-6). The strength of evidence for this outcome was low. The strength was downgraded due to risk of bias from the study design, as only one study was a true RCT (Marzo-Ortega et al., 2005), imprecision and inconsistency.

Three studies investigated the effect of TNFi on BMD at the *femoral neck*; studies were again not suitable for pooling due to significant heterogeneity (I^2=91%, Figure 7-7). Two studies found no significant effect of TNFi (Marzo-Ortega et al., 2005, Kang et al., 2013). Li et al (Li et al., 2015) found a beneficial effect of TNFi over SSZ (MD 14.5%, 95% CI 10.19 to 18.81). Strength of evidence was again low for this outcome, downgraded due to risk of bias, imprecision and inconsistency.

Two studies investigated the effect of TNFi on BMD of the *total hip* (Marzo-Ortega et al., 2005, Kang et al., 2013). Meta-analysis revealed no significant effect of TNFi on BMD of the total hip (MD -0.01, 95% CI -0.06 to 0.04; Figure 7-6). Strength of evidence was moderate, downgraded due to risk of bias from the study design.

Sensitivity analysis was performed for *lumbar spine* and *femoral neck* outcomes, removing a study (Li et al., 2015) which reported their results in percentage change only, in contrast to BMD values in the others. This reduced heterogeneity to 22% for lumbar spine and 0% for femoral neck. There were no significant between-group differences for BMD at spine or femoral neck (MD of 0.05, 95% CI -0.04 to 0.15, and MD of -0.01, 95% CI -0.07 to 0.04, respectively; see Figure 7-6).

In summary, there was moderate strength evidence for no significant difference between TNFi and controls in their effect on total hip BMD. Heterogeneity prevented pooling of studies to investigate the effect at lumbar spine and femoral neck in meta-analysis, with low strength evidence from narrative analysis not demonstrating an effect of TNFi. The current evidence does not support a recommendation for TNFi for treatment of low BMD at hip or spine in axSpA.

Figure 7-6: Forest plot demonstrating effect of TNFi on BMD (lumbar spine, femoral neck and total hip).

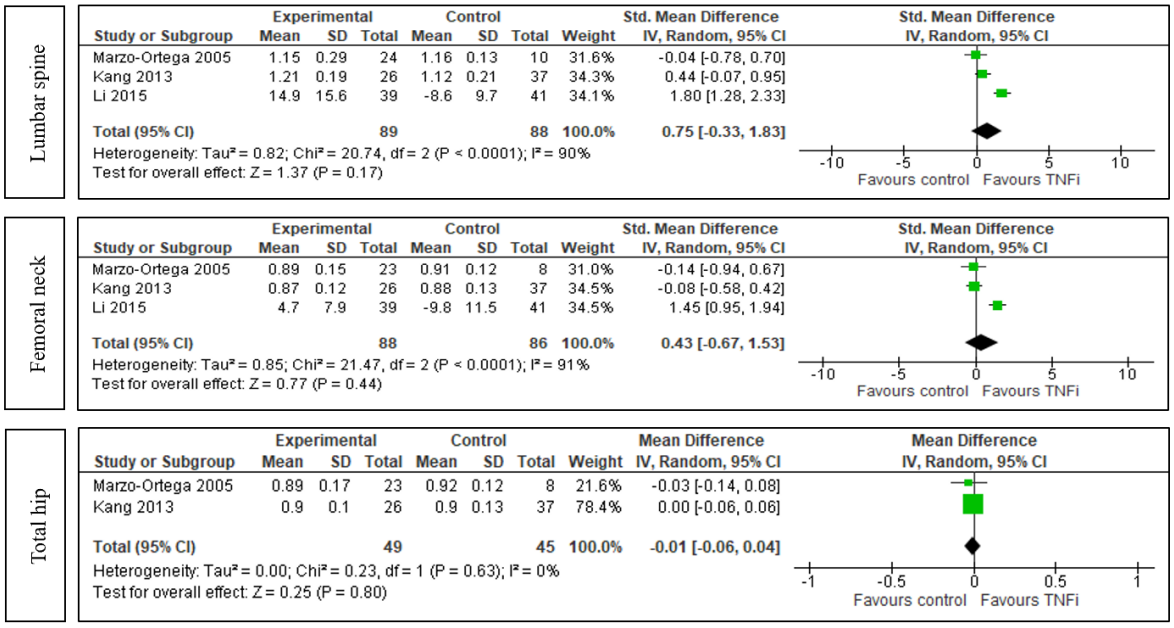
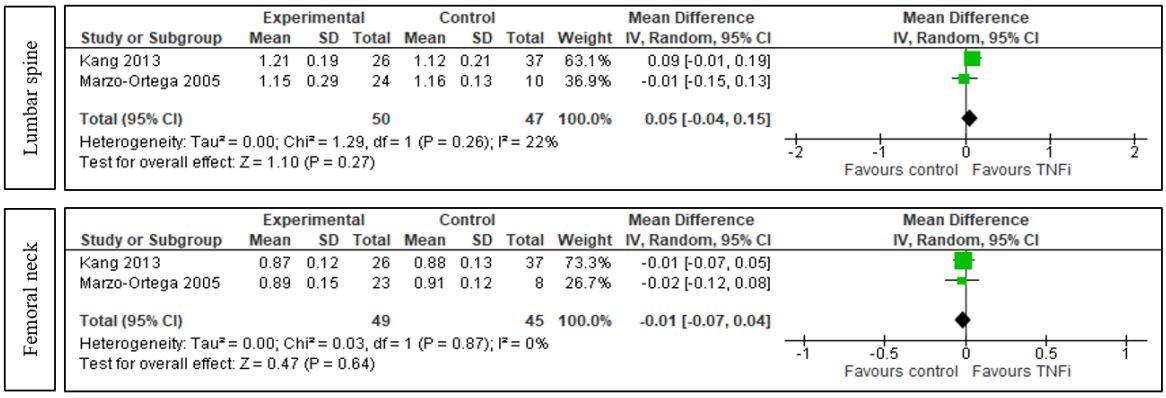


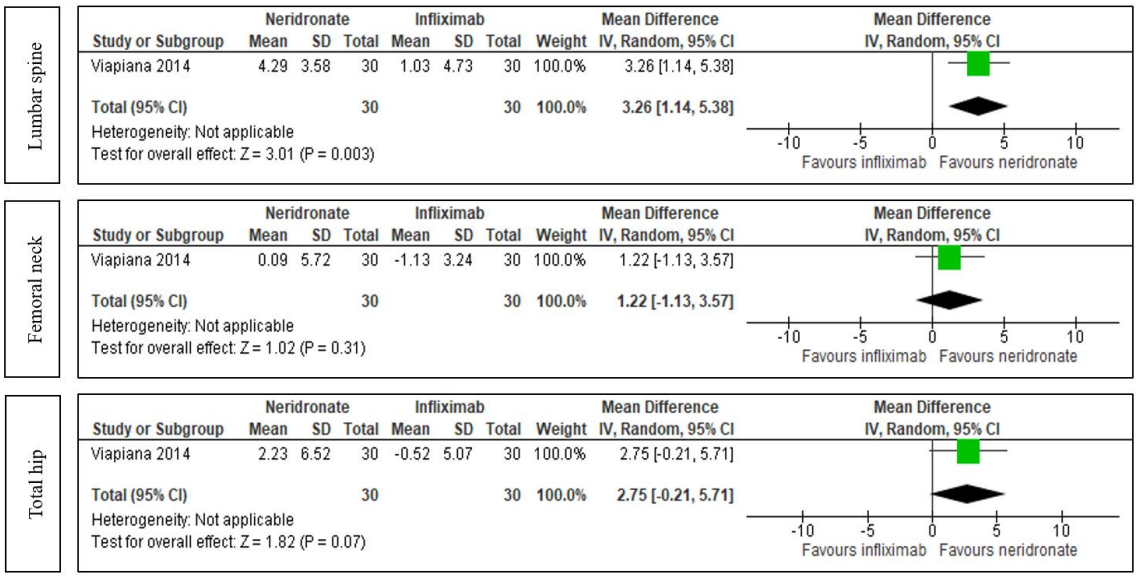
Figure 7-7: Forest plot demonstrating results of sensitivity analysis testing effect of TNFi on BMD (lumbar spine and femoral neck).



7.4.5.3 Comparison 3: Bisphosphonate versus TNFi

One study (Viapiana et al., 2014) compared the effect on BMD at *lumbar spine, femoral neck* and *total hip* of an intravenous bisphosphonate (neridronate) and infliximab. The results of the study showed a statistically significant effect on percentage change in BMD of the spine (MD 3.26, 95% CI 1.14 to 5.38; Figure 7-8) in favour of neridronate, but no effect on the percentage change in BMD of the femoral neck (MD 1.22, 95% CI -1.13 to 3.57) or total hip (MD 2.75, 95% CI -0.21 to 5.71). There was moderate strength of evidence for the lumbar spine outcome, downgraded due to the qRCT-design of the study, increasing the risk of bias. The strength of evidence was further downgraded for imprecision in the femoral neck and total hip outcomes. We conditionally recommend the use of IV neridronate for treatment of osteoporosis in axSpA.

Figure 7-8: Forest plot demonstrating effect of neridronate compared to infliximab on BMD (lumbar spine, femoral neck and total hip).



7.4.5.4 Comparison 4: Peloidotherapy versus standard therapy

Mihailov et al (Mihailov et al., 2015) aimed to report the efficacy of peloidotherapy on AS patients. However, results were only reported for those participants who received peloidotherapy; the manner in which the results are reported also prohibit any interpretation of their meaning. At the time of submission, no further information was available from the authors to bring any clarity. The risk of bias of this study was high, and the strength of evidence was very low. No recommendation can be made from this study.

A summary of the above recommendations can be found in Table 7-4.

Table 7-3: Summary of effects of interventions for each outcome, along with strength of evidence and strength/direction of recommendation.

Comparison		Outcome (BMD site)	Time point	N	Overall effect estimate MD (95% CI)	Heterogeneity			SoE	SoR	Studies
						x^2	p	I^2			
1	**Alendronate vs placebo or no treatment**	Lumbar spine	24m	180	4.22 (2.93 to 5.51)				++––[#,§]	NR	(Creamer et al., 2017)
			12m	24	-0.09 (-0.27 to 0.09)						(Khabbazi et al., 2014)
		Femoral neck	24m	180	2.01 (0.67 to 3.35)				+++–[†]	↑*	(Creamer et al., 2017)
		Total hip	24m	180	2.98 (2.05 to 3.91)				++––[#,§]	NR	(Creamer et al., 2017)
			12m	24	0.05 (-0.06 to 0.16)						(Khabbazi et al., 2014)
		Intertrochanteric hip	24m	180	3.70 (2.49 to 4.91)				+++–[†]	↑*	(Creamer et al., 2017)
	Alendronate + steroids vs standard treatment	Lumbar spine	12m	57	-0.71 (-1.55 to 0.13)				+–––[#,†a]	NR	(Soroush et al., 2016)
		Femoral neck	12m	57	-1.74 (-2.33 to -1.15)				+–––[#,†a]	NR	(Soroush et al., 2016)
2	**TNFi vs placebo or standard treatment**	Lumbar spine	30w	34	-0.01 (-0.15 to 0.13)				++––[#†§]	NR	(Marzo-Ortega et al., 2005)
			24m	63	0.09 (-0.01 to 0.19)						(Kang et al., 2013)
			52w	89	23.5 (17.77 to 29.23)						(Li et al., 2015)
		Sensitivity analysis	24m*	97	0.05 (-0.04 to 0.15)	1.29	0.26	22%	+++–[#]	NR	(Marzo-Ortega et al., 2005, Kang et al., 2013)
		Femoral neck	30w	31	-0.02 (-0.12 to 0.08)				++––[#†§]	NR	(Marzo-Ortega et al., 2005)
			24m	63	-0.01 (-0.07 to 0.05)						(Kang et al., 2013)
			52w	89	14.5 (10.19 to 18.81)						(Li et al., 2015)
		Sensitivity analysis	24m*	94	-0.01 (-0.07 to 0.04)	0.03	0.87	0%	+++–[#]	NR	(Kang et al., 2013, Marzo-Ortega et al., 2005)
		Total hip	24m[x]	94	-0.01 (-0.06 to 0.04)	0.23	0.63	0%	+++–[#]	NR	(Marzo-Ortega et al., 2005, Kang et al., 2013)
3	**Bisphosphonate vs TNFi**	Lumbar spine	6m	60	3.26 (1.14 to 5.38)				+++–[#]	↑*	(Viapiana et al., 2014)
		Femoral neck	6m	60	1.22 (-1.13 to 3.57)				++––[#†]	NR	(Viapiana et al., 2014)
		Total hip	6m	60	2.75 (-0.21 to 5.71)				++––[#†]	NR	(Viapiana et al., 2014)

++++ high level of evidence; +++− moderate level of evidence; ++−− low level of evidence; +−−− very low level of evidence; ↑ conditional recommendation for intervention. §Inconsistency; † Imprecision; # Limitations in the design and implementation; ‡standardised mean difference with 95% CI; ˣup to 24 months; a: serious limitations in the design and implementation of the study, warranting downgrading by two levels.*

BMD: bone mineral density; CI: confidence interval; m: months; N: number of participants; NR: no recommendation; SoE: strength of evidence; SoR: strength of recommendation; TNFi: tumour necrosis factor inhibitor; w: weeks.

Table 7-4: Summary of Recommendations.

Treatment	BMD site	Recommendation statement	SOR	SOE
Bisphosphonates	Lumbar spine	We recommend IV neridronate over infliximab for treatment of low BMD at lumbar spine	Conditional	Moderate
	Femoral neck	We recommend alendronate for treatment of low BMD	Conditional	Moderate
	Total hip	We make no recommendation regarding use of bisphosphonates	N/A	Moderate
TNF-inhibitors	Lumbar spine	We do not recommend the use of TNF-inhibitors for treatment of low BMD	N/A	Very low
	Femoral neck	We do not recommend the use of TNF-inhibitors for treatment of low BMD	N/A	Very low
	Total hip	We do not recommend the use of TNF-inhibitors for treatment of low BMD	N/A	Moderate

BMD: bone mineral density; N/A: not applicable; SOE: strength of evidence; SOR: strength of recommendation.

7.5 Discussion

7.5.1 Summary of main results

The aim of this systematic review was to assess the efficacy of pharmacological and non-pharmacological interventions on BMD in patients with axSpA. We wished to extract high-quality data, therefore included only RCTs and qRCTs in our review. We have summarised data from eight studies, all of which examined pharmacological interventions. No studies assessing non-pharmacological intervention on BMD were eligible for inclusion in our review.

We found two studies investigating the effect of alendronate on BMD compared to placebo or no treatment. Both studies investigated the impact of alendronate on the lumbar spine and total hip. There was clinical heterogeneity between the two studies, with Khabbazi et al (Khabbazi et al., 2014) reporting results on a younger population with earlier and more active disease than Creamer et al (Creamer et al., 2017). In addition, there was significant statistical heterogeneity. Thus, qualitative analysis was performed, without meta-analysis. We found no evidence favouring alendronate over placebo for treating BMD of the spine or total hip. There was moderate evidence to conditionally recommend the use of alendronate for treatment of low BMD at the femoral neck and intertrochanteric hip, with a small but clinically significant effect demonstrated. However, this recommendation is based on a single study, so caution is needed when interpreting the results (Creamer et al., 2017).

One further study investigated the effect of alendronate, but with methodological concerns (Soroush et al., 2016). In particular, steroids were used in a proportion of the intervention group and there were significant baseline differences between the groups. Therefore, it is not possible to isolate the effect of alendronate. The quality of evidence for this study is very low, prohibiting any clinically meaningful interpretation.

We found three studies which investigated the impact of TNFi on BMD (Li et al., 2015, Marzo-Ortega et al., 2005, Kang et al., 2013). There was minimal clinical heterogeneity between the studies. However, there was significant statistical heterogeneity for two of the outcomes (lumbar spine and femoral neck), due to differences in the reporting of results: two studies (Kang et al., 2013, Marzo-Ortega et al., 2005) reported absolute BMD values, whereas Li et al (Li et al., 2015) reported percentage change in BMD, prohibiting the pooling of studies for these outcomes. Narrative analysis revealed low level of evidence showing no difference between TNFi and controls on BMD. Sensitivity analysis removing the study with different reporting of results (Li

et al., 2015) confirmed this. Meta-analysis was possible for total hip BMD, with moderate evidence showing no effect of TNFi over standard therapy.

One study compared a bisphosphonate (IV neridronate) with a TNFi (Viapiana et al., 2014). There was moderate evidence to conditionally recommend IV neridronate over infliximab for BMD of the spine, but not the hip. However, caution is needed as this is based on one study. In addition, IV neridronate is currently licenced only in Italy, and not at all for osteoporosis. However, this is an interesting finding which should be investigated further with other forms of IV bisphosphonate.

The role non-pharmacological treatment has in treating osteoporosis and maintaining bone mass in the general population is well outlined (Howe et al., 2011). We were unable to find any studies fulfilling our eligibility criteria which investigated this in axSpA. Although Mihailov et al (Mihailov et al., 2015) purported to examine the effect of peloidotherapy in AS, including BMD as a secondary outcome measure, in reality the design of the study and the reporting of the results did not fulfil this aim. Considering the benefit of exercise shown in the general population (Howe et al., 2011), well-designed trials are needed to investigate the role in axSpA.

In order to comprehensively capture all studies which have investigated interventions on BMD in axSpA, we chose to include all follow-up lengths in our review. In the alendronate trials, follow-up varied from 12 to 24 months in duration. In the TNFi trials, one study reported a duration of 30 weeks (Marzo-Ortega et al., 2005) and the remaining two studies reported outcomes at 12 months (Li et al., 2015) and 24 months (Kang et al., 2013). The bisphosphonate versus TNFi trial (Viapiana et al., 2014) reported outcomes at six months. Experts recommend that BMD testing is performed 1-2 years after beginning treatment (Cosman et al., 2014). In order to detect a change in BMD, the change must be bigger than the precision error (least significant change, LSC) of the machine; therefore, changes in BMD of less than 3-6% at the hip and 2-4% at the spine may actually be due to the precision of testing and may not actually represent a significant change (Cosman et al., 2014). In the first few years after commencing treatment, there is also significant within-person variation, leading some authors to recommend against rechecking BMD in the first three years after commencing treatment, due to the potential for the results to mislead (Bell et al., 2009, Compston, 2009). Therefore, a negative result within a short follow-up period may not necessarily reflect a drug that does not work, merely that the duration of the trial was too short to see a positive result. It is likely that some of the studies included in this review had follow-up periods that are too short to definitively exclude a significant effect on BMD.

It is documented that assessing BMD in axSpA is challenging. In particular, it is accepted that conventional DXA can be inaccurate in assessing BMD of the lumbar spine, particularly when established disease is present (as detailed in previous chapters). All of the included studies assessed the lumbar spine using conventional PA DXA, which may not be sensitive enough to either detect osteoporosis or a change in BMD. As outlined in previous chapters, incorporating lateral DXA into the bone health assessment of adults with axSpA detects significantly more cases of low BMD than PA DXA, and is less affected by osteoproliferation. None of the studies eligible for this review included lateral DXA. Therefore, it is possible that significant effects were not detected due to suboptimal imaging techniques. Future studies should include lateral DXA when assessing the effect of treatment on BMD.

There were some differences in the populations included in each study in the review. All the studies included patients with AS according to mNY criteria (Soroush et al., 2016, Kang et al., 2013, Li et al., 2015, Marzo-Ortega et al., 2005, Viapiana et al., 2014, Mihailov et al., 2015), whereas only some studies also allowed patients that fulfilled ASAS criteria (Creamer et al., 2017, Khabbazi et al., 2014). No study exclusively examined patients according to ASAS criteria alone. Therefore, it was not possible to analyse patients with nr-axSpA separately to AS patients, something that would be interesting to focus on in future research.

The adherence rates with treatment were not reported in the majority of studies. It is good practice to report adherence in clinical trials (Chan et al., 2013). This is of particular importance in any trials with bisphosphonate medication, as it is well-known that adherence with osteoporosis treatment is extremely low (Cramer et al., 2007, Diez-Perez et al., 2017, Mikyas et al., 2014, Wu et al., 2016). Therefore, any future study examining the impact of treatment should have an objective and/or subjective measure of the adherence with treatment. There are different methods to measure this. The International Osteoporosis Foundation and European Calcified Tissue Society have recently issued recommendations for screening for oral bisphosphonates, through measuring bone turnover markers (Diez-Perez et al., 2017); this could be considered in any future trials.

7.5.2 Comparison with existing reviews

The effect of TNFi on BMD in AS was examined in 2014 in a systematic review by Haroon et al (Haroon et al., 2014), which found an effect favouring TNFi on lumbar spine and total hip BMD, as well as maintaining femoral neck BMD for up to two years. However, that review included both retrospective and prospective studies as they wished to assess the longitudinal effect of TNFi

on BMD, whereas we limited our analysis to RCTs and qRCTs in order to compare the effect to no/other treatment. In 2015, Siu et al (Siu et al., 2015) performed a meta-analysis of TNFi and steroids on BMD in RA and AS, which reported the results of two studies in AS. The duration of follow-up was 24-30 weeks and TNFi was associated with increased BMD at both the hip and spine. Our review includes more studies with longer duration and may account for the difference in effects.

To our knowledge, this is the first review to examine the impact of bisphosphonates on BMD in adults with axSpA.

7.5.3 Clinical implications

Treating osteoporosis in individuals with axSpA is a challenge for clinicians. The management of osteoporosis in this population was deemed outside the scope of the 2016 ASAS-EULAR management recommendations for axSpA (van der Heijde et al., 2017). Clinicians currently use those interventions which have an evidence base in the general population, such as exercise, bisphosphonates and denosumab. The results of this systematic review and meta-analysis highlight the lack of high-quality evidence available to clinicians when selecting treatments for individuals with axSpA.

The evidence conditionally supports clinicians in selecting alendronate for treatment of osteoporosis of the femoral neck in axSpA. However, decisions to use bisphosphonates for osteoporosis of the spine are not supported by the current body of evidence. Although IV neridronate was more effective than infliximab at the spine, this is not currently available for clinical use. Further research will be needed to determine if other formulations of IV bisphosphonates are effective for osteoporosis. TNF-inhibitors are commonly used in the management of axSpA for control of disease activity. The current balance of evidence doesn't support the use of TNF-inhibitors solely for the treatment of osteoporosis in this population.

7.5.4 Limitations

There are a number of limitations to this review. Many of the studies had missing data, that could not be obtained from the authors. Many of the studies did not have BMD as the primary outcome (Mihailov et al., 2015, Viapiana et al., 2014, Marzo-Ortega et al., 2005), therefore these studies may not have been powered adequately to detect a change. In addition, many of the studies had

very small numbers, again reducing the likelihood of seeing a significant change. Some studies had co-interventions (e.g. co-administration of calcium and/or vitamin D), which may confound results and lead to an over-estimation of the effect of the intervention. However, these co-interventions were only included if they were administered in both arms. Data extraction was performed by one author. Meta-analysis could not be performed in many of the outcomes due to heterogeneity. There was insufficient data available to assess the effect of individual TNFi. They were analysed together for the purpose of this review, to determine the class effect. We chose to prioritise the comparison of final BMD scores over percentage change from baseline, in-keeping with Cochrane recommendations (2011). However, there were studies where only percentage change was available, therefore the studies in this review contain a combination. Percentage change can sometimes give more exaggerated results than the final score, which can sometimes also lead to selective reporting and potential bias (2011).

7.5.5 Future research

This review highlights the absolute lack of high-quality evidence available to clinicians when attempting to treat osteoporosis, a condition that is known to occur at increased prevalence in axSpA. There is a strong case that more research is required into interventions to manage bone health in patients with axSpA. High-quality adequately-powered RCTs are urgently needed to fill this void. Future research should focus on:

1. the effect of bisphosphonates on BMD at the hip and spine
2. the effect of TNF-inhibitor on BMD at the hip and spine
3. the effect of exercise on BMD at the hip and spine.

Studies should be a minimum of two years in duration, and ideally longer. Adherence with the protocol should be measured. The superior effect of IV neridronate compared to infliximab is interesting and should be investigated further using licenced bisphosphonates and a longer follow-up period. Future studies investigating treatment of osteoporosis in axSpA should incorporate lateral DXA in their BMD assessment, to ensure that significant results are not missed due to suboptimal imaging techniques.

7.6 Conclusion

In summary, there is moderate level evidence to conditionally recommend the use of alendronate for the management of low BMD at femoral neck and intertrochanteric hip, but not spine, in

axSpA. The balance of evidence does not support a recommendation for the use of TNF-inhibitor in the management of low BMD. There is a lack of RCTs exploring the role of exercise in the management of BMD in this population. In contrast to the vast body of evidence available highlighting the benefit of pharmacological and non-pharmacological interventions on BMD in the general population, there is a paucity of good-quality evidence guiding clinicians managing bone health in axSpA. There is an urgent need to perform well-designed RCTs assessing the effect of both pharmacological and non-pharmacological interventions on bone health in axSpA.

Chapter 8 Discussion

8.1 Introduction

A detailed analysis of the findings of the four original studies and of the narrative and systematic reviews has been discussed in the relevant chapters (see Chapter 3 & Sections 2.4, 4.5, 5.5, 6.5, 7.5). In this chapter, the main findings from each study will be summarised and synthesised, the implications of these findings for clinical practice will be outlined and the limitations of the thesis will be acknowledged. Finally, future areas for research will be identified and discussed.

8.2 Summary of main findings

Existing literature has demonstrated that individuals with AxSpA have increased morbidity and mortality compared to age- and sex-matched controls (Chapter 1). ASAS-COMOSPA was a large multi-centric multinational cross-sectional study which aimed to describe the comorbidity profile of patients with axSpA (Molto et al., 2016). Osteoporosis was physician-reported as the most prevalent comorbidity in that study, affecting 13% of individuals. Ireland was not included as a country in the ASAS-COMOSPA study. Thus, it was not known if the profile of comorbidities seen in axSpA internationally was the same in the Irish cohort.

Comorbidity and multimorbidity are intimately linked. The presence of multimorbidity is known to be associated with worse outcomes, both in the general population and in RA (Radner et al., 2015c, Barnett et al., 2012), but had not yet been examined in axSpA. Therefore, the first aim of this thesis was to explore the profile of comorbid conditions that occur in individuals with axSpA and examine the prevalence of multimorbidity. Considering the high prevalence of osteoporosis seen in the ASAS-COMOSPA study, we also specifically aimed to examine the presence of osteoporosis in the population.

Study 1 was designed to explore these aims: a cross-sectional analysis of the ASRI cohort. Obesity was the most common comorbid condition in this analysis of ASRI, affecting 27% of the cohort. This is comparable to the general population, where 25% of adults ≥ 20 years of age in Ireland are obese (World Health Organization, 2013). Cardiovascular disease was also an important morbidity, with 30% of the cohort having at least one cardiovascular comorbidity. However, overt IHD was low, affecting only 3% of the study population. Cardiovascular disease is common in the general population in Ireland and is responsible for 35% of all deaths and 20%

of premature deaths (Cardiovascular Health Policy Group, 2010). Depression also featured prominently in the comorbidity profile, affecting 10% of the cohort. Accurate data on the prevalence of depression in the general population in Ireland is not available, although it has been shown to affect 12% of individuals over the age of 50 years (Briggs et al., 2018).

Over half (55%) of the cohort were multimorbid i.e. had one or more conditions in addition to axSpA. Individuals with multimorbidity had more severe disease than those without, with a combination of objective and subjective disease outcome measures used. Some disease outcome measures (BASMI, HAQ and BASFI) continued to worsen the more comorbid conditions an individual had. However, BASDAI and ASQoL were higher in multimorbid individuals, with no subsequent worsening the higher the number of comorbid conditions affecting a person. Individuals with multimorbidity were a mean of ten years older than those without; however, the mean age of multimorbid individuals was only 50 years.

The prevalence of reported osteoporosis (i.e. diagnosis prior to enrolment in ASRI) in the whole cohort was only 5%. However, less than 20% of the cohort had previously had an objective measure of their BMD; analysis of the available DXA results in this subgroup revealed a much higher prevalence of osteoporosis (23%). This suggested that osteoporosis is a frequent, yet under-recognised, comorbidity in axSpA. This unexpectedly high prevalence of osteoporosis could be explained by selection bias, as individuals with risk factors may have been more likely to undergo DXA assessment. Therefore, whether this figure reflected the true prevalence of osteoporosis in adults with axSpA in Ireland could not be identified from Study 1. More data on the epidemiology of osteoporosis in axSpA in Ireland was needed.

The results from Study 1 identified the need for a narrative review of the literature examining osteoporosis in axSpA. This review was presented in Chapter 3 and highlighted the inconsistencies across studies regarding osteoporosis in this population. The prevalence of low BMD varied widely in the studies, ranging from 4% to 58%, as outlined in Table 3-1 of Chapter 3. An examination of the risk factors for low BMD in axSpA highlighted the lack of knowledge in this area. The balance of evidence suggested that more severe disease is a risk factor for low BMD in axSpA, but other risk factors for osteoporosis were more difficult to identify. Published systematic reviews have established an increased prevalence of vertebral fractures in axSpA, but no clear association between BMD and vertebral fractures has been definitively demonstrated.

The narrative review also established that the current gold standard technique for assessing BMD is inaccurate in axSpA, due to the osteoproliferation that occurs in the spine to a variable degree in axSpA. This osteoproliferation can hinder the accuracy of PA DXA, by allowing BMD of the

lumbar spine to be over-estimated, potentially missing existing osteoporosis. Lateral DXA of the lumbar spine was identified as a promising technique, which is unaffected by the osteoproliferation. However, the usefulness of incorporating lateral DXA into the BMD assessment of individuals with axSpA has not been tested.

Biomarkers have been shown to predict fragility fractures in postmenopausal women and have the potential to be a clinically useful tool. The use of biomarkers in identifying individuals with axSpA who are at risk of developing osteoporosis has not been tested.

The outcome of the narrative review was the generation of a number of research questions, which formed the basis of the subsequent studies.

The cross-sectional Study 2 was designed to primarily compare lateral DXA with PA DXA in their ability to assess BMD of the spine, using this data to examine the prevalence of osteoporosis in individuals with axSpA and explore associations with BMD. The results of this study demonstrated that lateral BMD of the lumbar spine was significantly lower than PA DXA. Incorporating lateral DXA into the BMD assessment of included individuals significantly increased the detection of low BMD from 35% to 58%. Osteoproliferation, as measured by mSASSS, interfered with the ability of PA DXA to accurately assess BMD. This was the first study to demonstrate that incorporating lateral DXA in the assessment of BMD in axSpA increased the detection of low BMD.

Subsequently, the associations with osteoporosis in axSpA were explored. A sub-group of men above the age of 50 years and postmenopausal women were analysed in this study, in-keeping with ISCD guidelines regarding the diagnosis of osteoporosis (Shepherd et al., 2015). The results demonstrated that more women than men had low BMD. Additionally, the prevalence of low BMD was higher in patients who were HLA-B27 positive, a finding that has not been demonstrated in humans previously. There was no relationship between the presence of low BMD and any disease severity measures.

Study 3 aimed to assess relationships between BMD and biomarkers in individuals with axSpA. Specifically, we studied bone turnover markers (CTX, osteocalcin, P1NP), vitamin D, serum urate and testosterone. Increased bone turnover was correlated with lower BMD at all sites, testosterone was inversely correlated with BMD at PA spine only and higher serum urate was associated with higher BMD. There was no relationship between vitamin D and BMD. However, the relationships between biomarkers and osteoporosis were attenuated and lost statistical significance once controlled for important confounders. Therefore, none of the biomarkers tested

in this study were independently associated with low BMD and therefore are not of clinical use in identifying patients with osteoporosis. Interestingly, lower testosterone levels were associated more severe disease in men, and independently predicted active disease and worse quality of life. This is the first study to demonstrate this.

Study 4 aimed to determine whether QUS of the calcaneus could be used as a triage tool for osteoporosis in individuals with axSpA, thus reducing the need for DXA assessment in this population. This would have important clinical implications, as DXA is a limited resource. QUS was selected as the tool due to its portability and ease of use, making it suitable for use in an outpatient setting, as well as its ability to predict fractures in post-menopausal women (Section 6-1). The results of this study demonstrated that QUS of the calcaneus could be used as a triage tool to identify with 90% confidence individuals with axSpA at **low risk** of having low BMD. This would negate the need for onward DXA referral in the identified individuals. This strategy had the ability to save up to 27% of DXAs in this population. QUS was not suitable to identify individuals at high-risk of osteoporosis.

The final step in this thesis was to examine treatment options for individuals with osteoporosis in axSpA. However, a literature search revealed a lack of recommendations guiding clinicians in this area, representing an unmet need. Therefore, the aim of Study 5 was to systematically appraise and synthesise RCTs and qRCTS examining the efficacy of pharmacological and non-pharmacological interventions on BMD in adults with axSpA. Eight studies met the inclusion criteria for the study, all testing pharmacological interventions, with no RCTs or qRCTs examining non-pharmacological interventions identified. Moderate level evidence supported a conditional recommendation for the use of alendronate for low BMD of the femoral neck and IV neridronate over infliximab for low BMD of the lumbar spine. However, caution is needed, as only one study formed the basis for each of these recommendations. The balance of evidence did not support the use of TNFi at either spine or hip. Clinical and statistical heterogeneity prevented pooling of many of the studies. There is a lack of high-quality studies guiding clinicians when treating osteoporosis in individuals with axSpA.

8.3 Clinical implications

8.3.1 Comorbidities: a profile of individuals with axSpA

Comorbidities are common in individuals with axSpA. This has been demonstrated internationally in the COMOSPA study (Molto et al., 2016) and confirmed by the cross-sectional

analysis of ASRI, presented in Chapter 2. Obesity was the most common comorbidity in our cohort, affecting 27% of individuals with axSpA. Obesity is known to be important in multimorbidity in the general population (Agborsangaya et al., 2013) and is associated with higher mortality (Flegal et al., 2013). The prospective longitudinal Groningen Leeuwarden Axial SpA (GLAS) cohort also demonstrated a high prevalence of obesity in axSpA, affecting 22% of the cohort (Maas et al., 2016).

Considering the global obesity epidemic (World Health Organization, 2013), this is an important finding. Obesity was only recognised as a disease in 2013 (Kyle et al., 2016), therefore clinicians don't often regard it as a comorbid condition in its own right. The high prevalence amongst individuals with axSpA has important clinical implications. Further research will be required to determine the cause of obesity in individuals with axSpA. This research should explore if this prevalence merely reflects background obesity trends or if it is a result of improved treatments, negating the need for exercise that individuals with axSpA previously required to function. Longitudinal analysis will better answer these questions.

Almost a third (30%) of the ASRI cohort had at least one cardiovascular comorbidity. Whilst the prevalence of overt ischaemic heart disease was low, affecting 3% of the individuals, hypertension and hyperlipidaemia affected 21% and 16% of the cohort, respectively. These conditions are both comorbid conditions in their own right, as well as conditions that increase the risk for IHD. This has important clinical implications, with the knowledge that AS is associated with increased vascular mortality (Haroon et al., 2015). Therefore, clinicians should actively screen adults with axSpA attending their clinics for evidence of CV morbidity. Although assessing for screening practice was not an outcome in our study, other studies have demonstrated that screening for comorbidities is suboptimal (Molto et al., 2016).

8.3.2 Multimorbidity in axSpA: a real concern

Multimorbidity is a relatively new concept in rheumatology, and describes a model of care whereby the patient, rather than the index disease, is placed at the centre of care (see Chapter 1). Multimorbidity is common in individuals with axSpA, affecting 55% of the cohort (Study 1). Individuals with multimorbidity were on average ten years older than individuals without multimorbidity; however, the mean age of the multimorbid group was only 50 years. This is a clinically relevant finding. Multimorbidity is often considered an issue isolated to the elderly, with the bulk of research in the general population performed in individuals over the age of 65 years (Navickas et al., 2016). Therefore, clinicians with responsibility for individuals with axSpA

should begin to consider multimorbidity in this population at an earlier age than the general population.

Study 1 also demonstrated that individuals with axSpA who are multimorbid have worse outcomes than those with axSpA alone. More research is needed to determine whether the more severe disease seen in multimorbid individuals with axSpA is cause or effect; however, until this issue is clarified, clinicians should recognise that multimorbid individuals have worse outcomes and may require more resources to control their disease. Therefore, clinicians should be actively screening individuals with axSpA attending their clinics for multimorbidity.

It is well-recognised that individuals with multimorbidity have complex needs, requiring cohesive individualised patient-centred strategies, rather than traditional disease-focused models of care (Navickas et al., 2016, Radner et al., 2014). Clinicians should be striving to improve an individual's overall function, not merely focusing on the outcomes of only one condition. This may impact on a clinician's choice of treatment strategies, with multidisciplinary approaches becoming more important in the context of multimorbidity.

8.3.3 Osteoporosis in axSpA: *when* should we screen?

An important take-home point from the cross-sectional analysis of ASRI presented in Chapter 2 (Study 1) is that screening for osteoporosis is low in individuals with axSpA in Ireland. Less than 20% of individuals enrolled in ASRI had ever had an objective assessment of BMD.

This raises the important question of when to begin screening for low BMD in this population. There is no consensus in the literature on when screening for osteoporosis should occur in individuals with axSpA. In the general population, screening is recommended when women reach the age of 65 and men the age of 70 years (Shepherd et al., 2015). However, the ISCD also recommend that 'adults with a disease or condition associated with low bone mass or bone loss' undergo BMD testing (Shepherd et al., 2015). Study 1 indicated that axSpA is associated with low bone mass, considering the 23% prevalence of osteoporosis in individuals who had undergone DXA testing. Study 2 confirmed that 18% of individuals had osteoporosis at either the hip or spine and 58% had BMD lower than expected for age. Therefore, the results of both these studies provide evidence that axSpA is a condition associated with low bone mass. Applying ISCD guidelines, active screening for low BMD should begin from diagnosis.

8.3.4 Osteoporosis in axSpA: *how* should we screen?

Traditional BMD assessment involves the use of PA DXA to assess the lumbar spine and hip (Shepherd et al., 2015). The narrative review presented in Chapter 3 outlines why this traditional technique is insufficient to accurately assess BMD in individuals with axSpA. Study 2 confirms that osteoproliferation interferes with PA DXA assessment of the lumbar spine. The more severe the osteoproliferation, the less likely low BMD will be detected. Lateral DXA significantly increased the detection of low BMD in individuals with axSpA, compared to PA DXA alone (Study 2). Therefore, clinicians managing the bone health of individuals with axSpA should ensure that lateral DXA is incorporated into the BMD assessment from the first time they undergo DXA assessment. Clinicians should no longer be relying solely on conventional DXA techniques, as to do so will miss a significant proportion of individuals affected by low bone mass.

Clinicians also need to consider that it is not merely osteoporosis that should be considered. In the general population, it is well known that more fractures occur in individuals with BMD in the osteopenia range rather than the osteoporosis range (Section 1.13). The ISCD have now recommended that 'low bone mass' or 'low bone density' are the preferred terms over osteopenia (Shepherd et al., 2015). Therefore, clinicians should be looking for low bone density in individuals with axSpA, not merely osteoporosis. Lateral DXA can assist in this.

8.3.5 Vertebral fractures in axSpA: osteoporosis or osteoproliferation?

The literature supports the statement that vertebral fractures occur at an increased prevalence in individuals with axSpA. However, risk factors for vertebral fractures in this population are much less clear.

The prevalence of vertebral fractures was low (n=4) in Study 2, limiting our ability to progress comprehension of the link between vertebral fractures and BMD in axSpA. BMD of the spine was higher when measured by PA DXA in those with vertebral fractures than those without. Yet, lateral and hip DXA were not significantly different. Considering that PA DXA is affected by osteoproliferation, whereas lateral and hip DXA are a better reflection of BMD, this may suggest that osteoproliferation, i.e. structural damage, is more important in the pathogenesis of vertebral fractures than low BMD. This is supported by the finding that mSASSS was also higher, although not statistically significantly, in individuals with vertebral fractures.

As a direct result of the low prevalence of vertebral fractures in Study 2, there is not enough evidence to draw definitive conclusions. Importantly, the lack of an association between fractures and BMD in this study cannot discount the potential role that BMD may play in the aetiology of

vertebral fractures in individuals with axSpA, particularly considering the strong association shown in the general population. However, clinicians should also consider the possibility that the risk of vertebral fractures is associated with osteoproliferation and investigate for vertebral fractures if individuals with syndesmophytes complain of increased back pain.

8.3.6 Osteoporosis in axSpA: can we use biomarkers for diagnosis?

Biomarkers are useful in a number of situations. Indeed, in axSpA, the presence of HLA-B27 is a clinically useful biomarker in diagnosing the condition (Danve and O'Dell, 2015). In postmenopausal women, BTMs are useful for predicting future fracture risk. This was the rationale in Study 3 to examine the role of biomarkers in detecting osteoporosis in individuals with axSpA, recognising that this could be a clinically useful tool for clinicians. Unfortunately, although many of the biomarkers tested did correlate significantly with BMD, none had an independent relationship. Therefore, none of biomarkers tested can currently be used to identify individuals with osteoporosis.

No definitive relationships were detected between any of the biomarkers tested and vertebral fractures in Study 3. Interestingly, although there was no independent link between testosterone and BMD, men who had a previous history of any fracture had lower testosterone levels than those without a history of fracture and there was a non-significant lower testosterone level in men with vertebral fractures compared to those without. This finding certainly needs to be investigated further.

The low prevalence of vertebral fractures in the study means that significant relationships between vertebral fractures and biomarkers cannot be out-ruled and the analysis will need to be performed again in a cohort with a higher prevalence of fractures to definitively establish the presence or lack of relationships.

8.3.7 The role of testosterone in disease activity

Although it was not a primary outcome of Study 3, associations between testosterone levels and disease activity were witnessed in men. Lower testosterone was independently associated with a higher odds of active disease. Lower levels were also associated with worse function and more disability, along with more severe spinal restriction.

As this is a cross-sectional analysis, associations can be established, but causality cannot be commented upon. Therefore, whether the low testosterone is the cause of more active disease or

the effect cannot be identified from this study. Testosterone is an easy-to-measure variable in clinical practice and testosterone replacement therapy is used in a number of conditions. However, the results of this study alone are insufficient to currently recommend that testosterone replacement should be considered, but future research will hopefully allow us to understand the role of testosterone in disease activity.

8.3.8 Osteoporosis in axSpA: can we triage individuals?

Considering the young age of onset in axSpA, affected individuals are often working full-time, therefore limiting unnecessary hospital attendances would be beneficial. In addition, strain on DXA resources means there can be long wait times for bone health assessment. Therefore, ensuring only appropriate individuals are referred for DXA assessment would be useful. If we accept that in line with ISCD guidelines individuals with axSpA should be undergoing BMD assessment from close to diagnosis (Shepherd et al., 2015), then a triage tool which could be implemented in routine clinical care and had the ability to stratify patients according to their risk of having low BMD would be clinically, and likely economically, beneficial. QUS of the calcaneus is one such tool.

Study 4 demonstrated that a triage programme using QUS of the calcaneus can identify with 90% confidence an individual that **does not** have low BMD. This is a clinically useful finding. The ability to confidently identify this cohort would avoid the need for onward DXA referral, saving up to 27% of DXAs. QUS was not useful in identifying individuals at risk of having osteoporosis.

There are some limitations to this triage strategy which prohibit its immediate widespread clinical use. Specific device thresholds must be derived for each machine, which should be validated against DXA, as in Study 4. In addition, a cost-effectiveness analysis should be carried out. However, the results of Study 4 suggest that implementing the use of QUS of the calcaneus as a triage tool for osteoporosis would be clinically useful in the management of individuals with axSpA.

8.3.9 Osteoporosis in axSpA: how do we treat?

Study 5 was the first study to critically synthesise the available evidence regarding all treatment options for osteoporosis occurring in individuals with axSpA. The results of the systematic review and meta-analysis have important clinical implications.

Currently, clinicians are treating osteoporosis in axSpA according to guidelines that exist primarily for post-menopausal women and older men, as there are no specific guidelines in axSpA (van der Heijde et al., 2017). Therefore, medications such as bisphosphonates and denosumab are being used for the treatment of low BMD in individuals with axSpA. Based on the available evidence from Study 5, clinicians can use alendronate for treatment of low BMD of the femoral neck with some confidence. The sole other treatment with evidence supporting its use is IV neridronate, a medication that is not licenced in many countries.

This review emphasised the lack of high-quality studies investigating the use and efficacy of these treatments in axSpA and a complete absence of RCTs investigating non-pharmacological options. This has important clinical implications as it highlights a huge gap in the literature. Clinicians treating osteoporosis in axSpA are doing so without very little evidence supporting their treatment options. It is undeniable that osteoporosis is prevalent in axSpA. Therefore, effective treatments are needed which have a supporting evidence base. Well-designed trials are urgently needed that will answer these questions.

8.4 Limitations of the thesis

Each chapter individually acknowledged limitations specific to that study (see Sections 2.4.3, 4.5.1, 5.5.4, 6.5.1 & 7.5.4). This section aims to summarise further limitations which apply to the body of work as a whole.

Studies 1-4 in this thesis were all cross-sectional in design. There are automatic limitations associated with the cross-sectional design of a study, in particular that cause-and-effect cannot be established. However, cross-sectional studies are very important in progressing research agendas, as they allow associations and relationships to be explored, which then allows further research questions to be generated. This has been demonstrated throughout the thesis. Cross-sectional studies are also useful for providing epidemiological information, allowing the scale of a problem to be identified. Through the cross-sectional studies presented in this thesis, a definite high prevalence of osteoporosis affecting individuals with axSpA in Ireland was identified. In addition, we established an improved technique to assess BMD. These findings have important clinical implications, as outlined in the preceding section. Further research questions have also been generated.

The overall prevalence of fragility fractures was low in this thesis. Whilst this is reassuring for the included individuals with axSpA, the low prevalence limited investigation into the aetiology

of vertebral fractures in axSpA. However, by recruiting individuals consecutively from rheumatology clinics and databases, we ensured that the included participants were representative of the overall population. Had we specifically recruited individuals with fractures, this would have amounted to selection bias, skewing in particular the epidemiological results regarding osteoporosis prevalence. Therefore, the aetiology of vertebral fractures will need to be addressed in specific studies in the future.

The population presented in Study 1 (ASRI cohort) is representative of the whole country of Ireland, as individuals are enrolled from many centres spanning all parts of the country. In contrast, selection bias may have existed for Studies 2-4. Individuals were enrolled from St. James's Hospital and Tallaght Hospital. These catchment areas have specific cultural, environmental and socio-economic properties that may limit extrapolation of the findings to different areas. However, both hospitals contain a mixed caseload of urban and rural populations. We also attempted to limit selection bias as outlined in Section 4.1.6. Therefore, it is expected that this cohort is basically representative of the national population.

Analysis of the epidemiology of osteoporosis was limited to post-menopausal women and men over the age of 50 years. The decision to do this was made as T scores are not recommended to be used in individuals outside this population. When using Z scores to assess BMD, different categories are defined: 'below the expected range for age' or 'within the expected range for age' (Shepherd et al., 2015). These differences in categories prohibited grouping of the two populations together. In addition, Z scores were not available for lateral DXA, due to a lack of a reference database. Therefore, many of the findings are limited to postmenopausal women and men over the age of 50 years and cannot be easily extrapolated to younger individuals. However, our findings are more robust as a result of adopting this approach. In addition, osteoporosis is known to occur predominantly in older individuals in the general population, so the need to understand osteoporosis in the context of axSpA is most pressing in our chosen population. The comparison of lateral and PA DXA in assessing BMD of the spine applies to the whole cohort, including premenopausal women and younger men.

8.5 Future research directions

This thesis has explored comorbidity and multimorbidity in axSpA, specifically focusing on osteoporosis: assessment, epidemiology, screening and treatment. There are a number of further research agendas that should now be pursued.

Study 1 was the first to highlight the prevalence of multimorbidity in axSpA and demonstrate its negative impact on disease outcomes. This is certainly an interesting topic that deserves more research. The prevalence of multimorbidity needs to be investigated in other cohorts, to determine if these figures are reproduced. Longitudinal analysis of the development of multimorbidity in individuals with axSpA should be performed, as this will develop a clearer picture of cause and effect. Of particular interest is the question whether multimorbidity leads to more severe disease or whether it is active disease over time which leads to the development of multimorbidity. Identifying risk factors for developing multimorbidity would also be interesting, providing clinically useful information to physicians taking control of the care of individuals with axSpA.

It is now established that comorbidities are prevalent in individuals with axSpA. Longitudinal analysis is required, again to determine the cause and effect pattern. In addition, the effect of treatment of axSpA on the development of comorbidities is an unmet need, as is the effect of controlling comorbid conditions on the morbidity and mortality of axSpA. Whether implementing a patient-centred model of care leads to better outcomes than the current disease-focused model is unknown and could be answered with a well-designed RCT.

An interesting finding presented in Study 1 was the high prevalence of obesity in the ASRI cohort. Osteoporosis was selected as the focus of the remainder of the thesis; however, obesity in axSpA deserves similar investigation. One interesting question to be answered is whether the prevalence of obesity merely reflects the background obesity trends of a country. With the advances in treatment over the years, many of the symptoms of axSpA, such as back stiffness and pain, are much better controlled, possibly negating the need for exercise that individuals with axSpA previously required to function – longitudinal analysis will better answer these questions.

The impact of obesity in axSpA should be explored. In particular, the effect of treating obesity on axSpA should be delineated, particularly with exercise and lifestyle modification interventions. Physical exercise is included as a key recommendation in the management of axSpA throughout the disease (van der Heijde et al., 2017). However, knowledge of and adherence to physical activity guidelines is low in individuals with rheumatic disease (O'Dwyer et al., 2014), with fewer than half of individuals meeting physical activity guidelines (O'Dwyer et al., 2015). A behavioural change intervention was shown to improve physical activity in individuals with axSpA (O'Dwyer et al., 2017). The impact of a similar intervention on BMI would be an interesting research question.

This thesis has extensively explored the topic of osteoporosis in individuals with axSpA. Perhaps of most importance is the demonstration that lateral DXA can be used to accurately assess BMD

of the spine in this population. To ensure that this technique becomes a routine part of axSpA care, continued investigation into the use of lateral DXA is needed. Study 2 was a cross-sectional study; the performance of lateral DXA when longitudinally analysing BMD of the spine needs to be investigated. Also, whether lateral DXA has the ability to detect improvements in BMD from treatment interventions is unknown.

The relationship between BMD and fragility fractures, particularly vertebral fractures, could not be defined in this thesis. However, the results of Study 2 suggested that osteoproliferation may play a role in the pathophysiology of the disease. This represents an urgent unmet need in individuals with axSpA, considering the known risk of vertebral fractures in this cohort, with the potential for devastating neurological outcomes. It is crucial to understand the cause of the fractures, to allow effective screening and preventative measures be put in place. A case-control cohort study would allow this question to be answered, whereby individuals with vertebral and other fragility fractures are recruited, matched to controls and the association with BMD and structural damage established. However, in order to avoid missing a significant relationship, BMD tools should be used which can recognise osteoporosis in the context of osteoproliferation. Therefore, lateral DXA should be incorporated into the BMD assessment in any such study. QCT is an alternative tool that could be used in a research setting.

Biomarkers were not found to have a role in the prediction of osteoporosis in adults with axSpA in this thesis. However, they may have a role in fragility fracture prediction, particularly considering the non-significant differences noted in testosterone levels between those with and without vertebral fractures. In a cohort of individuals with a higher prevalence of fractures, biomarkers should be investigated to determine their role in fracture prediction.

Study 4 presented a triage tool which could identify, with 90% confidence, individuals with low risk of having low BMD, thus reducing the need for DXA. This is a strategy which could be introduced into clinical practice. However, prior to this happening, a cost-effective analysis of the strategy should be carried out. Investigating the use of QUS in fracture prediction in this population should also be performed.

As outlined in Section 4.1.5, epidemiology of low BMD was focused on postmenopausal women and men over the age of 50 years. A reference database of the BMD of the lateral spine of 'normal' young controls should be established to allow the calculation of Z scores. This would allow accurate epidemiology of low BMD to be obtained in younger cohorts. In addition, the role of QUS in this population could then be tested.

TBS was introduced in Section 1.14.3 and is an exciting new development in the assessment of BMD. This could not be investigated in this thesis, as the equipment was not available in the BMD testing centre in St. James's Hospital. However, this technique should be explored in individuals with axSpA.

Perhaps the most pressing need identified from this thesis is the treatment of osteoporosis in axSpA. The systematic review and meta-analysis presented in Study 5 highlighted the lack of RCT evidence available to clinicians when considering the treatment of osteoporosis. Bisphosphonates remain the most common pharmacological treatment modality for osteoporosis. There is extensive data available for post-menopausal women, with a long duration of follow-up, regarding the beneficial effects of bisphosphonates. Although denosumab is a newer treatment, there is also an extensive body of evidence supporting its use in the general population. This body of evidence is needed in axSpA. Knowledge of the use of teriparatide is limited to case reports, where it has been suggested to cause healing of fractures (Biro et al., 2017). However, whether it is safe to use an anabolic agent in a disease characterised by osteoproliferation is unknown, as is its effect on BMD and fracture rate.

The results presented in the systematic review highlighted the complete lack of RCTs investigating the role of non-pharmacological interventions on BMD in axSpA. In postmenopausal women, exercise has a positive impact on BMD (Howe et al., 2011). The impact of falls interventions on fracture reduction is also unknown in axSpA.

Therefore, high-quality RCTs are urgently needed to fill this void. The effect of both pharmacological and non-pharmacological interventions should be studied. To ensure that significant relationships are not missed, adequate follow-up times are required. Studies should be continued for a minimum of two years, and ideally longer. Adequate DXA assessment tools should be used. The impact of interventions on BMD is important, but data regarding the impact of treatment on the occurrence of fractures is also needed. Therefore, fracture incidence should be included as a study end-point in any study investigating interventions. Pharmacological interventions should include bisphosphonates, both oral and IV, as well as denosumab and teriparatide.

Chapter 9 Conclusion

Comorbidity is a key issue in axSpA, with affected individuals suffering from increased morbidity and mortality compared to age- and sex-matched controls. Osteoporosis was reported as the most prevalent comorbid condition in a large international cross-sectional study of individuals with axSpA. The profile of comorbidities in individuals with axSpA in Ireland has not previously been investigated; specifically, the prevalence of osteoporosis was unknown. Therefore, the aim of this thesis was to examine comorbidity in adults with axSpA in Ireland, with a specific focus on osteoporosis.

Cross-sectional Study 1 of ASRI established that comorbidity and multimorbidity were prevalent in individuals with axSpA, with affected adults suffering from more severe disease. Screening for osteoporosis was low amongst individuals with axSpA, but the prevalence of low BMD was high amongst those who had undergone screening. A comprehensive narrative review of the literature regarding osteoporosis in axSpA highlighted that detecting osteoporosis in this population is challenging. The challenges arise from the inherent pathophysiology of axSpA, leading to variable degrees of osteoproliferation of the spine. This can falsely raise the BMD when assessed using conventional PA DXA of the spine. Cross-sectional Study 2 demonstrated that lateral DXA was significantly lower than conventional PA DXA when assessing BMD of the spine. The difference was most marked in individuals with more severe structural damage. Using lateral DXA in the osteoporosis assessment significantly increased the prevalence of low BMD and osteoporosis. Clinicians should routinely incorporate lateral DXA when assessing the BMD of individuals with axSpA.

Low BMD in this population affected more women than men, but was not associated with the severity of disease in Study 2. SUA has previously been shown to protect against osteoporosis in AS; however, in Study 3, the correlation between SUA and BMD was attenuated when confounding factors were controlled for. No clinically useful biomarkers which could identify individuals with low BMD were found in this study.

There was no definite association between BMD and vertebral fractures, but the number of fragility fractures in this population was small. However, there was a suggestion in Study 2 that the prevalence of vertebral fractures was higher in those with more severe structural damage of the spine. In addition, Study 3 demonstrated that testosterone levels were lower in men with fractures. Both of these findings are interesting, but caution is required when interpreting them,

due to the low prevalence of fractures. Larger cohorts of individuals with fractures are needed to investigate this finding further.

Considering the prevalence of osteoporosis in adults with axSpA, screening for osteoporosis should begin early in the disease course, in-line with ISCD recommendations. In Study 4, QUS of the calcaneus confidently out-ruled individuals with low BMD, thus negating the need for onward DXA referral in adults with values above the device-specific thresholds established in this study. Therefore, QUS is a promising tool which could be incorporated into the bone health assessment of individuals with axSpA.

The evidence base supporting the use of treatment interventions on BMD in axSpA is limited. Study 5 demonstrated that there were no RCTs investigating the effect of non-pharmacological interventions on BMD in axSpA. There is moderate evidence to conditionally support the use of alendronate for treatment of osteoporosis of the femoral neck and IV neridronate for treatment of osteoporosis of the lumbar spine. No RCTs exist to support the use of other pharmacological treatments for low BMD in individuals with axSpA. There is a need to undertake high-quality RCTs to investigate the impact of interventions, both pharmacological and non-pharmacological, on BMD in adults with axSpA.

Chapter 10 References

1993. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *American Journal of Medicine,* 94**,** 646-50.

1994. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. *World Health Organization Technical Report Series,* 843**,** 1-129.

2011. *Cochrane Handbook for Systematic Reviews of Interventions*.

ABRAHAMSEN, B., VAN STAA, T., ARIELY, R., OLSON, M. & COOPER, C. 2009. Excess mortality following hip fracture: a systematic epidemiological review. *Osteoporosis International,* 20**,** 1633-50.

AGBORSANGAYA, C. B., NGWAKONGNWI, E., LAHTINEN, M., COOKE, T. & JOHNSON, J. A. 2013. Multimorbidity prevalence in the general population: the role of obesity in chronic disease clustering. *BMC Public Health,* 13**,** 1161.

AGGARWAL, R., RINGOLD, S., KHANNA, D., NEOGI, T., JOHNSON, S. R., MILLER, A., BRUNNER, H. I., OGAWA, R., FELSON, D., OGDIE, A., ALETAHA, D. & FELDMAN, B. M. 2015. Distinctions between diagnostic and classification criteria? *Arthritis Care & Research,* 67**,** 891-7.

AHMED, N., PRIOR, J. A., CHEN, Y., HAYWARD, R., MALLEN, C. D. & HIDER, S. L. 2016. Prevalence of cardiovascular-related comorbidity in ankylosing spondylitis, psoriatic arthritis and psoriasis in primary care: a matched retrospective cohort study. *Clinical Rheumatology,* 35**,** 3069-3073.

AKGOL, G., KAMANLI, A. & OZGOCMEN, S. 2014. Evidence for inflammation-induced bone loss in non-radiographic axial spondyloarthritis. *Rheumatology (Oxford, England),* 53**,** 497-501.

AKHTER, M. P. & JUNG, L. K. 2007. Decreased bone strength in HLA-B27 transgenic rat model of spondyloarthropathy. *Rheumatology (Oxford, England),* 46**,** 1258-62.

AKKOC, N. 2008. Are spondyloarthropathies as common as rheumatoid arthritis worldwide? A review. *Current Rheumatology Reports,* 10**,** 371-8.

AKKOC, N., YARKAN, H., KENAR, G. & KHAN, M. A. 2017. Ankylosing Spondylitis: HLA-B*27-Positive Versus HLA-B*27-Negative Disease. *Current Rheumatology Reports,* 19**,** 26.

AL-ARFAJ, A. 1996. Profile of ankylosing spondylitis in Saudi Arabia. *Clinical Rheumatology,* 15**,** 287-9.

AL-SARI, U. A., TOBIAS, J. & CLARK, E. 2016. Health-related quality of life in older people with osteoporotic vertebral fractures: a systematic review and meta-analysis. *Osteoporosis International,* 27**,** 2891-900.

ALMEIDA, M., HAN, L., MARTIN-MILLAN, M., O'BRIEN, C. A. & MANOLAGAS, S. C. 2007. Oxidative stress antagonizes Wnt signaling in osteoblast precursors by diverting beta-catenin from T cell factor- to forkhead box O-mediated transcription. *Journal of Biological Chemistry,* 282**,** 27298-305.

ALMIRALL, J. & FORTIN, M. 2013. The coexistence of terms to describe the presence of multiple concurrent diseases. *J Comorb,* 3**,** 4-9.

AMES, B. N., CATHCART, R., SCHWIERS, E. & HOCHSTEIN, P. 1981. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. *Proceedings of the National Academy of Sciences of the United States of America,* 78**,** 6858-62.

AMOR, B., DOUGADOS, M. & MIJIYAWA, M. 1990. [Criteria of the classification of spondylarthropathies]. *Revue du Rhumatisme et des Maladies Osteo-Articulaires,* 57**,** 85-9.

ANAGNOSTIS, P., PASCHOU, S. A., MINTZIORI, G., CEAUSU, I., DEPYPERE, H., LAMBRINOUDAKI, I., MUECK, A., PEREZ-LOPEZ, F. R., REES, M., SENTURK, L. M., SIMONCINI, T., STEVENSON, J. C., STUTE, P., TREMOLLIERES, F. A. & GOULIS, D. G. 2017. Drug holidays from bisphosphonates and denosumab in postmenopausal osteoporosis: EMAS position statement. *Maturitas,* 101**,** 23-30.

ANDREWS, E. B., GILSENAN, A. W., MIDKIFF, K., SHERRILL, B., WU, Y., MANN, B. H. & MASICA, D. 2012. The US postmarketing surveillance study of adult osteosarcoma and teriparatide: study design and findings from the first 7 years. *Journal of Bone and Mineral Research,* 27**,** 2429-37.

ANDREWS, J., GUYATT, G., OXMAN, A. D., ALDERSON, P., DAHM, P., FALCK-YTTER, Y., NASSER, M., MEERPOHL, J., POST, P. N., KUNZ, R., BROZEK, J., VIST, G., RIND, D., AKL, E. A. & SCHUNEMANN, H. J. 2013a. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *Journal of Clinical Epidemiology,* 66**,** 719-25.

ANDREWS, J. C., SCHUNEMANN, H. J., OXMAN, A. D., POTTIE, K., MEERPOHL, J. J., COELLO, P. A., RIND, D., MONTORI, V. M., BRITO, J. P., NORRIS, S., ELBARBARY, M., POST, P., NASSER, M., SHUKLA, V., JAESCHKE, R., BROZEK, J., DJULBEGOVIC, B. & GUYATT, G. 2013b. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *Journal of Clinical Epidemiology,* 66**,** 726-35.

AOUAD, K., ZIADE, N. & BARALIAKOS, X. 2019. Structural progression in axial spondyloarthritis. *Joint, Bone, Spine: Revue du Rhumatisme*.

APPEL, H., MAIER, R., LODDENKEMPER, C., KAYSER, R., MEIER, O., HEMPFING, A. & SIEPER, J. 2010. Immunohistochemical analysis of osteoblasts in zygapophyseal joints of patients with ankylosing spondylitis reveal repair mechanisms similar to osteoarthritis. *Journal of Rheumatology,* 37**,** 823-8.

ARENDS, S., BROUWER, E., EFDE, M., VAN DER VEER, E., BOOTSMA, H., WINK, F. & SPOORENBERG, A. 2017. Long-term drug survival and clinical effectiveness of etanercept treatment in patients with ankylosing spondylitis in daily clinical practice. *Clinical and Experimental Rheumatology,* 35**,** 61-68.

ARENDS, S., SPOORENBERG, A., BRUYN, G. A., HOUTMAN, P. M., LEIJSMA, M. K., KALLENBERG, C. G., BROUWER, E. & VAN DER VEER, E. 2011. The relation between bone mineral density, bone turnover markers, and vitamin D status in ankylosing spondylitis patients with active disease: a cross-sectional analysis. *Osteoporosis International,* 22**,** 1431-9.

ARENDS, S., SPOORENBERG, A., EFDE, M., BOS, R., LEIJSMA, M. K., BOOTSMA, H., VEEGER, N. J., BROUWER, E. & VAN DER VEER, E. 2014. Higher bone turnover is related to spinal radiographic damage and low bone mineral density in ankylosing spondylitis patients with active disease: a cross-sectional analysis. *PloS One,* 9**,** e99685.

ARIAS, E., HERON, M. & XU, J. 2017. United States Life Tables, 2013. *National Vital Statistics Reports,* 66**,** 1-64.

ARMAGAN, B., SARI, A., ERDEN, A., KILIC, L., ERDAT, E. C., KILICKAP, S., KIRAZ, S., BILGEN, S. A., KARADAG, O., AKDOGAN, A., ERTENLI, I. & KALYONCU, U. 2018. Starting of biological disease modifying antirheumatic drugs may be postponed in rheumatoid arthritis patients with multimorbidity: Single center real life results. *Medicine (Baltimore),* 97**,** e9930.

ARONSON, J. K. & FERNER, R. E. 2017. Biomarkers-A General Review. *Current Protocols in Pharmacology,* 76**,** 9.23.1-9.23.17.

BAKLAND, G., GRAN, J. T. & NOSSENT, J. C. 2011. Increased mortality in ankylosing spondylitis is related to disease activity. *Annals of the Rheumatic Diseases,* 70**,** 1921-5.

BARALIAKOS, X., HAIBEL, H., FRITZ, C., LISTING, J., HELDMANN, F., BRAUN, J. & SIEPER, J. 2013. Long-term outcome of patients with active ankylosing spondylitis with etanercept-sustained efficacy and safety after seven years. *Arthritis Research & Therapy,* 15**,** R67.

BARALIAKOS, X., HELDMANN, F., CALLHOFF, J., LISTING, J., APPELBOOM, T., BRANDT, J., VAN DEN BOSCH, F., BREBAN, M., BURMESTER, G., DOUGADOS, M., EMERY, P., GASTON, H., GRUNKE, M., VAN DER HORST-BRUINSMA, I. E., LANDEWE, R., LEIRISALO-REPO, M., SIEPER, J., DE VLAM, K., PAPPAS, D., KILTZ, U., VAN DER HEIJDE, D. & BRAUN, J. 2014. Which spinal lesions are associated with new bone formation in patients with ankylosing spondylitis treated with anti-TNF agents? A long-term observational study using MRI and conventional radiography. *Annals of the Rheumatic Diseases,* 73**,** 1819-25.

BARALIAKOS, X., KILTZ, U., PETERS, S., APPEL, H., DYBOWSKI, F., IGELMANN, M., KALTHOFF, L., KRAUSE, D., MENNE, H. J., SARACBASI-ZENDER, E., SCHMITZ-BORTZ, E., VIGNESWARAN, M. & BRAUN, J. 2017. Efficiency of treatment with non-steroidal anti-inflammatory drugs according to current recommendations in patients with radiographic and non-radiographic axial spondyloarthritis. *Rheumatology (Oxford, England),* 56**,** 95-102.

BARALIAKOS, X., KIVITZ, A. J., DEODHAR, A. A., BRAUN, J., WEI, J. C., DELICHA, E. M., TALLOCZY, Z. & PORTER, B. 2018. Long-term effects of interleukin-17A inhibition with secukinumab in active ankylosing spondylitis: 3-year efficacy and safety results from an extension of the Phase 3 MEASURE 1 trial. *Clinical and Experimental Rheumatology,* 36**,** 50-55.

BARNETT, K., MERCER, S. W., NORBURY, M., WATT, G., WYKE, S. & GUTHRIE, B. 2012. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet,* 380**,** 37-43.

BARRIONUEVO, P., KAPOOR, E., ASI, N., ALAHDAB, F., MOHAMMED, K., BENKHADRA, K., ALMASRI, J., FARAH, W., SARIGIANNI, M., MUTHUSAMY,

K., AL NOFAL, A., HAYDOUR, Q., WANG, Z. & MURAD, M. H. 2019. Efficacy of Pharmacological Therapies for the Prevention of Fractures in Postmenopausal Women: A Network Meta-Analysis. *Journal of Clinical Endocrinology and Metabolism,* 104**,** 1623-1630.

BEAUDOIN, C., JEAN, S., BESSETTE, L., STE-MARIE, L. G., MOORE, L. & BROWN, J. P. 2016. Denosumab compared to other treatments to prevent or treat osteoporosis in individuals at risk of fracture: a systematic review and meta-analysis. *Osteoporosis International,* 27**,** 2835-2844.

BELL, K. J., HAYEN, A., MACASKILL, P., IRWIG, L., CRAIG, J. C., ENSRUD, K. & BAUER, D. C. 2009. Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data. *BMJ,* 338**,** b2266.

BERINGER, T. R., FINCH, M., MC, A. T. H., WHITEHEAD, E., KEEGAN, D. A., KELLY, J., LEE, G., MCKANE, R., MCNALLY, C. & MCQUILKEN, M. 2005. A study of bone mineral density in women with forearm fracture in Northern Ireland. *Osteoporosis International,* 16**,** 430-4.

BESSANT, R., HARRIS, C. & KEAT, A. 2003. Audit of the diagnosis, assessment, and treatment of osteoporosis in patients with ankylosing spondylitis. *Journal of Rheumatology,* 30**,** 779-82.

BHALA, N., EMBERSON, J., MERHI, A., ABRAMSON, S., ARBER, N., BARON, J. A., BOMBARDIER, C., CANNON, C., FARKOUH, M. E., FITZGERALD, G. A., GOSS, P., HALLS, H., HAWK, E., HAWKEY, C., HENNEKENS, C., HOCHBERG, M., HOLLAND, L. E., KEARNEY, P. M., LAINE, L., LANAS, A., LANCE, P., LAUPACIS, A., OATES, J., PATRONO, C., SCHNITZER, T. J., SOLOMON, S., TUGWELL, P., WILSON, K., WITTES, J. & BAIGENT, C. 2013. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet,* 382**,** 769-79.

BHATIA, K., PRASAD, M. L., BARNISH, G. & KOKI, G. 1988. Antigen and haplotype frequencies at three human leucocyte antigen loci (HLA-A, -B, -C) in the Pawaia of Papua New Guinea. *American Journal of Physical Anthropology,* 75**,** 329-40.

BIRO, I., BUBBEAR, J., DONNELLY, S., FATTAH, Z., SARKODIEH, J., RANGANATHAN, A. & TAHIR, H. 2017. Teriparatide and vertebral fracture healing in Ankylosing Spondylitis. *Trauma Case Rep,* 12**,** 34-39.

BLACK, D. M., CUMMINGS, S. R., KARPF, D. B., CAULEY, J. A., THOMPSON, D. E., NEVITT, M. C., BAUER, D. C., GENANT, H. K., HASKELL, W. L., MARCUS, R., OTT, S. M., TORNER, J. C., QUANDT, S. A., REISS, T. F. & ENSRUD, K. E. 1996. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *The Lancet,* 348**,** 1535-1541.

BLACK, D. M., DELMAS, P. D., EASTELL, R., REID, I. R., BOONEN, S., CAULEY, J. A., COSMAN, F., LAKATOS, P., LEUNG, P. C., MAN, Z., MAUTALEN, C., MESENBRINK, P., HU, H., CAMINIS, J., TONG, K., ROSARIO-JANSEN, T., KRASNOW, J., HUE, T. F., SELLMEYER, D., ERIKSEN, E. F. & CUMMINGS, S. R. 2007. Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis. *New England Journal of Medicine,* 356**,** 1809-1822.

BLACK, D. M., GREENSPAN, S. L., ENSRUD, K. E., PALERMO, L., MCGOWAN, J. A., LANG, T. F., GARNERO, P., BOUXSEIN, M. L., BILEZIKIAN, J. P. & ROSEN,

C. J. 2003. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *New England Journal of Medicine,* 349**,** 1207-15.

BLACK, D. M. & ROSEN, C. J. 2016. Clinical Practice. Postmenopausal Osteoporosis. *New England Journal of Medicine,* 374**,** 254-62.

BLACK, D. M., SCHWARTZ, A. V., ENSRUD, K. E., CAULEY, J. A., LEVIS, S., QUANDT, S. A., SATTERFIELD, S., WALLACE, R. B., BAUER, D. C., PALERMO, L., WEHREN, L. E., LOMBARDI, A., SANTORA, A. C., CUMMINGS, S. R. & FLEX RESEARCH GROUP, F. T. 2006. Effects of Continuing or Stopping Alendronate After 5 Years of TreatmentThe Fracture Intervention Trial Long-term Extension (FLEX): A Randomized Trial. *JAMA,* 296**,** 2927-2938.

BLACK, D. M., THOMPSON, D. E., BAUER, D. C., ENSRUD, K., MUSLINER, T., HOCHBERG, M. C., NEVITT, M. C., SURYAWANSHI, S. & CUMMINGS, S. R. 2000. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. *Journal of Clinical Endocrinology and Metabolism,* 85**,** 4118-24.

BLAKE, G. M., JAGATHESAN, T., HERD, R. J. & FOGELMAN, I. 1994. Dual X-ray absorptiometry of the lumbar spine: the precision of paired anteroposterior/lateral studies. *British Journal of Radiology,* 67**,** 624-30.

BLUMBERG, B. S. 1958. Bernard Connor's description of the pathology of ankylosing spondylitis. *Arthritis and Rheumatism,* 1**,** 553-63.

BODINE, P. V. & KOMM, B. S. 2006. Wnt signaling and osteoblastogenesis. *Reviews in Endocrine & Metabolic Disorders,* 7**,** 33-9.

BODIS, G., TOTH, V. & SCHWARTING, A. 2018. Role of Human Leukocyte Antigens (HLA) in Autoimmune Diseases. *Rheumatology and therapy,* 5**,** 5-20.

BOLAND, E. W. 1961. Rheumatoid spondylitis. *Arthritis and Rheumatism,* 4**,** 645-8.

BOLLAND, M. J., GREY, A., AVENELL, A., GAMBLE, G. D. & REID, I. R. 2011. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ,* 342**,** d2040.

BONE, H. G., WAGMAN, R. B., BRANDI, M. L., BROWN, J. P., CHAPURLAT, R., CUMMINGS, S. R., CZERWINSKI, E., FAHRLEITNER-PAMMER, A., KENDLER, D. L., LIPPUNER, K., REGINSTER, J. Y., ROUX, C., MALOUF, J., BRADLEY, M. N., DAIZADEH, N. S., WANG, A., DAKIN, P., PANNACCIULLI, N., DEMPSTER, D. W. & PAPAPOULOS, S. 2017. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol,* 5**,** 513-523.

BOONEN, A., BRAUN, J., VAN DER HORST BRUINSMA, I. E., HUANG, F., MAKSYMOWYCH, W., KOSTANJSEK, N., CIEZA, A., STUCKI, G. & VAN DER HEIJDE, D. 2010. ASAS/WHO ICF Core Sets for ankylosing spondylitis (AS): how to classify the impact of AS on functioning and health. *Annals of the Rheumatic Diseases,* 69**,** 102-7.

BOUXSEIN, M. L. & RADLOFF, S. E. 1997. Quantitative ultrasound of the calcaneus reflects the mechanical properties of calcaneal trabecular bone. *Journal of Bone and Mineral Research,* 12**,** 839-46.

BOWNESS, P. 2015. HLA-B27. *Annual Review of Immunology,* 33**,** 29-48.

BRANDT, J., HAIBEL, H., CORNELY, D., GOLDER, W., GONZALEZ, J., REDDIG, J., THRIENE, W., SIEPER, J. & BRAUN, J. 2000. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab. *Arthritis and Rheumatism,* 43**,** 1346-52.

BRANDT, J., KHARIOUZOV, A., LISTING, J., HAIBEL, H., SORENSEN, H., RUDWALEIT, M., SIEPER, J. & BRAUN, J. 2004. Successful short term treatment of patients with severe undifferentiated spondyloarthritis with the anti-tumor necrosis factor-alpha fusion receptor protein etanercept. *Journal of Rheumatology,* 31**,** 531-8.

BRAUN, J., BARALIAKOS, X., DEODHAR, A., BAETEN, D., SIEPER, J., EMERY, P., READIE, A., MARTIN, R., MPOFU, S. & RICHARDS, H. B. 2017. Effect of secukinumab on clinical and radiographic outcomes in ankylosing spondylitis: 2-year results from the randomised phase III MEASURE 1 study. *Annals of the Rheumatic Diseases,* 76**,** 1070-1077.

BRAUN, J., BARALIAKOS, X., KILTZ, U., HELDMANN, F. & SIEPER, J. 2015. Classification and diagnosis of axial spondyloarthritis--what is the clinically relevant difference? *Journal of Rheumatology,* 42**,** 31-8.

BRAUN, J., DEODHAR, A., DIJKMANS, B., GEUSENS, P., SIEPER, J., WILLIAMSON, P., XU, W., VISVANATHAN, S., BAKER, D., GOLDSTEIN, N. & VAN DER HEIJDE, D. 2008. Efficacy and safety of infliximab in patients with ankylosing spondylitis over a two-year period. *Arthritis and Rheumatism,* 59**,** 1270-8.

BRAUN, J., PHAM, T., SIEPER, J., DAVIS, J., VAN DER LINDEN, S., DOUGADOS, M. & VAN DER HEIJDE, D. 2003. International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. *Annals of the Rheumatic Diseases,* 62**,** 817-24.

BRAUN, J. & PINCUS, T. 2002. Mortality, course of disease and prognosis of patients with ankylosing spondylitis. *Clinical and Experimental Rheumatology,* 20**,** S16-22.

BRAUN, J., VAN DEN BERG, R., BARALIAKOS, X., BOEHM, H., BURGOS-VARGAS, R., COLLANTES-ESTEVEZ, E., DAGFINRUD, H., DIJKMANS, B., DOUGADOS, M., EMERY, P., GEHER, P., HAMMOUDEH, M., INMAN, R. D., JONGKEES, M., KHAN, M. A., KILTZ, U., KVIEN, T., LEIRISALO-REPO, M., MAKSYMOWYCH, W. P., OLIVIERI, I., PAVELKA, K., SIEPER, J., STANISLAWSKA-BIERNAT, E., WENDLING, D., OZGOCMEN, S., VAN DROGEN, C., VAN ROYEN, B. & VAN DER HEIJDE, D. 2011. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Annals of the Rheumatic Diseases,* 70**,** 896-904.

BREBAN, M., VIGNON, E., CLAUDEPIERRE, P., DEVAUCHELLE, V., WENDLING, D., LESPESSAILLES, E., EULLER-ZIEGLER, L., SIBILIA, J., PERDRIGER, A., MEZIERES, M., ALEXANDRE, C. & DOUGADOS, M. 2002. Efficacy of infliximab in refractory ankylosing spondylitis: results of a six-month open-label study. *Rheumatology (Oxford, England),* 41**,** 1280-5.

BREMANDER, A., PETERSSON, I. F., BERGMAN, S. & ENGLUND, M. 2011. Population-based estimates of common comorbidities and cardiovascular disease in ankylosing spondylitis. *Arthritis Care & Research,* 63**,** 550-6.

BRIGGS, R., TOBIN, K., KENNY, R. A. & KENNELLY, S. P. 2018. What is the prevalence of untreated depression and death ideation in older people? Data from the Irish Longitudinal Study on Aging. *International Psychogeriatrics,* 30**,** 1393-1401.

BRINCAT, M., GAMBIN, J., BRINCAT, M. & CALLEJA-AGIUS, J. 2015. The role of vitamin D in osteoporosis. *Maturitas,* 80**,** 329-32.

BRIOT, K., DURNEZ, A., PATERNOTTE, S., MICELI-RICHARD, C., DOUGADOS, M. & ROUX, C. 2013. Bone oedema on MRI is highly associated with low bone mineral density in patients with early inflammatory back pain: results from the DESIR cohort. *Annals of the Rheumatic Diseases,* 72**,** 1914-9.

BRIOT, K., GEUSENS, P., EM BULTINK, I., LEMS, W. F. & ROUX, C. 2017. Inflammatory diseases and bone fragility. *Osteoporosis International,* 28**,** 3301-3314.

BROWN, M. A., KENNEDY, L. G., MACGREGOR, A. J., DARKE, C., DUNCAN, E., SHATFORD, J. L., TAYLOR, A., CALIN, A. & WORDSWORTH, P. 1997. Susceptibility to ankylosing spondylitis in twins: the role of genes, HLA, and the environment. *Arthritis and Rheumatism,* 40**,** 1823-8.

BROWN, W. M. & DOLL, R. 1965. Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis. *British Medical Journal,* 2**,** 1327-32.

BUSCHIAZZO, E. A., SCHNEEBERGER, E. E., SOMMERFLECK, F. A., LEDESMA, C. & CITERA, G. 2016. Mortality in patients with ankylosing spondylitis in Argentina. *Clinical Rheumatology,* 35**,** 2229-33.

CAI, G., WANG, L., FAN, D., XIN, L., LIU, L., HU, Y., DING, N., XU, S., XIA, G., JIN, X., XU, J., ZOU, Y. & PAN, F. 2015. Vitamin D in ankylosing spondylitis: review and meta-analysis. *Clinica Chimica Acta,* 438**,** 316-22.

CALIN, A., GARRETT, S., WHITELOCK, H., KENNEDY, L. G., O'HEA, J., MALLORIE, P. & JENKINSON, T. 1994. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *Journal of Rheumatology,* 21**,** 2281-5.

CALIN, A., PORTA, J., FRIES, J. F. & SCHURMAN, D. J. 1977. Clinical history as a screening test for ankylosing spondylitis. *JAMA,* 237**,** 2613-4.

CALLHOFF, J., SIEPER, J., WEISS, A., ZINK, A. & LISTING, J. 2015. Efficacy of TNFalpha blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. *Annals of the Rheumatic Diseases,* 74**,** 1241-8.

CAMACHO, P. M., PETAK, S. M., BINKLEY, N., CLARKE, B. L., HARRIS, S. T., HURLEY, D. L., KLEEREKOPER, M., LEWIECKI, E. M., MILLER, P. D., NARULA, H. S., PESSAH-POLLACK, R., TANGPRICHA, V., WIMALAWANSA, S. J. & WATTS, N. B. 2016. American association of clinical endocrinologists and american college of endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis - 2016. *Endocrine Practice,* 22**,** 1-42.

CAPACI, K., HEPGULER, S., ARGIN, M. & TAS, I. 2003. Bone mineral density in mild and advanced ankylosing spondylitis. *Yonsei Medical Journal,* 44**,** 379-84.

CARDIOVASCULAR HEALTH POLICY GROUP 2010. Changing cardiovascular health: national cardovascular health policy 2010-2019. *In:* CHILDREN, H. A. (ed.). Government Publications.

CARTER, S. & LORIES, R. J. 2011. Osteoporosis: a paradox in ankylosing spondylitis. *Curr Osteoporos Rep,* 9**,** 112-5.

CASSELL, A., EDWARDS, D., HARSHFIELD, A., RHODES, K., BRIMICOMBE, J., PAYNE, R. & GRIFFIN, S. 2018. The epidemiology of multimorbidity in primary care: a retrospective cohort study. *British Journal of General Practice*.

CAULEY, J. A., CHLEBOWSKI, R. T., WACTAWSKI-WENDE, J., ROBBINS, J. A., RODABOUGH, R. J., CHEN, Z., JOHNSON, K. C., O'SULLIVAN, M. J., JACKSON, R. D. & MANSON, J. E. 2013. Calcium plus vitamin D supplementation and health outcomes five years after active intervention ended: the Women's Health Initiative. *J Womens Health (Larchmt),* 22**,** 915-29.

CAULEY, J. A., EWING, S. K., TAYLOR, B. C., FINK, H. A., ENSRUD, K. E., BAUER, D. C., BARRETT-CONNOR, E., MARSHALL, L. & ORWOLL, E. S. 2010. Sex steroid hormones in older men: longitudinal associations with 4.5-year change in hip bone mineral density--the osteoporotic fractures in men study. *Journal of Clinical Endocrinology and Metabolism,* 95**,** 4314-23.

CAULEY, J. A., ROBBINS, J., CHEN, Z., CUMMINGS, S. R., JACKSON, R. D., LACROIX, A. Z., LEBOFF, M., LEWIS, C. E., MCGOWAN, J., NEUNER, J., PETTINGER, M., STEFANICK, M. L., WACTAWSKI-WENDE, J. & WATTS, N. B. 2003. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA,* 290**,** 1729-38.

CAVANI, F., GIAVARESI, G., FINI, M., BERTONI, L., DE TERLIZZI, F., BARKMANN, R. & CANE, V. 2008. Influence of density, elasticity, and structure on ultrasound transmission through trabecular bone cylinders. *IEEE Trans Ultrason Ferroelectr Freq Control,* 55**,** 1465-72.

CENTER, J. R., BLIUC, D., NGUYEN, T. V. & EISMAN, J. A. 2007. Risk of subsequent fracture after low-trauma fracture in men and women. *JAMA,* 297**,** 387-94.

CHAN, A.-W., TETZLAFF, J. M., ALTMAN, D. G., LAUPACIS, A., GØTZSCHE, P. C., KRLEŽA-JERIĆ, K., HRÓBJARTSSON, A., MANN, H., DICKERSIN, K., BERLIN, J. A., DORÉ, C. J., PARULEKAR, W. R., SUMMERSKILL, W. S. M., GROVES, T., SCHULZ, K. F., SOX, H. C., ROCKHOLD, F. W., RENNIE, D. & MOHER, D. 2013. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. *Annals of Internal Medicine,* 158**,** 200-207.

CHANDRAN, S., ALDEI, A., JOHNSON, S. R., CHEUNG, A. M., SALONEN, D. & GLADMAN, D. D. 2016. Prevalence and risk factors of low bone mineral density in psoriatic arthritis: A systematic review. *Seminars in Arthritis and Rheumatism,* 46**,** 174-82.

CHEN, B., CHENG, G., WANG, H. & FENG, Y. 2016. Increased risk of vertebral fracture in patients with rheumatoid arthritis: A meta-analysis. *Medicine (Baltimore),* 95**,** e5262.

CHIN, K. Y. & IMA-NIRWANA, S. 2013. Calcaneal quantitative ultrasound as a determinant of bone health status: what properties of bone does it reflect? *International Journal of Medical Sciences,* 10**,** 1778-83.

CHOI, Y., WOO, K. M., KO, S. H., LEE, Y. J., PARK, S. J., KIM, H. M. & KWON, B. S. 2001. Osteoclastogenesis is enhanced by activated B cells but suppressed by activated CD8(+) T cells. *European Journal of Immunology,* 31**,** 2179-88.

CHRISTENSEN, K., DOBLHAMMER, G., RAU, R. & VAUPEL, J. W. 2009. Ageing populations: the challenges ahead. *The Lancet,* 374**,** 1196-1208.

CHRISTIANSEN, A. A., HENDRICKS, O., KUETTEL, D., HORSLEV-PETERSEN, K., JURIK, A. G., NIELSEN, S., RUFIBACH, K., LOFT, A. G., PEDERSEN, S. J., HERMANSEN, L. T., OSTERGAARD, M., ARNBAK, B., MANNICHE, C. & WEBER, U. 2017. Limited Reliability of Radiographic Assessment of Sacroiliac Joints in Patients with Suspected Early Spondyloarthritis. *Journal of Rheumatology,* 44**,** 70-77.

CIUREA, A., SCHERER, A., EXER, P., BERNHARD, J., DUDLER, J., BEYELER, B., KISSLING, R., STEKHOVEN, D., RUFIBACH, K., TAMBORRINI, G., WEISS, B., MULLER, R., NISSEN, M. J., MICHEL, B. A., VAN DER HEIJDE, D., DOUGADOS, M., BOONEN, A. & WEBER, U. 2013. Tumor necrosis factor alpha inhibition in radiographic and nonradiographic axial spondyloarthritis: results from a large observational cohort. *Arthritis and Rheumatism,* 65**,** 3096-106.

CLOWES, J. A., PEEL, N. F. & EASTELL, R. 2006. Device-specific thresholds to diagnose osteoporosis at the proximal femur: an approach to interpreting peripheral bone measurements in clinical practice. *Osteoporosis International,* 17**,** 1293-302.

COATES, L., PACKHAM, J. C., CREAMER, P., HAILWOOD, S., BHALLA, A. S., CHAKRAVARTY, K., MULHERIN, D., TAYLOR, G., MATTEY, D. L. & BHALLA, A. K. 2017. Clinical efficacy of oral alendronate in ankylosing spondylitis: a randomised placebo-controlled trial. *Clinical and Experimental Rheumatology,* 35**,** 445-451.

COATES, L. C., CAWKWELL, L. S., NG, N. W., BENNETT, A. N., BRYER, D. J., FRASER, A. D., EMERY, P. & MARZO-ORTEGA, H. 2008. Real life experience confirms sustained response to long-term biologics and switching in ankylosing spondylitis. *Rheumatology (Oxford, England),* 47**,** 897-900.

COFFRE, M., ROUMIER, M., RYBCZYNSKA, M., SECHET, E., LAW, H. K., GOSSEC, L., DOUGADOS, M., BIANCHI, E. & ROGGE, L. 2013. Combinatorial control of Th17 and Th1 cell functions by genetic variations in genes associated with the interleukin-23 signaling pathway in spondyloarthritis. *Arthritis and Rheumatism,* 65**,** 1510-21.

COIFFIER, G., BOUVARD, B., CHOPIN, F., BIVER, E., FUNCK-BRENTANO, T., GARNERO, P. & GUGGENBUHL, P. 2013. Common bone turnover markers in rheumatoid arthritis and ankylosing spondylitis: a literature review. *Joint, Bone, Spine: Revue du Rhumatisme,* 80**,** 250-7.

COLBERT, R. A., TRAN, T. M. & LAYH-SCHMITT, G. 2014. HLA-B27 misfolding and ankylosing spondylitis. *Molecular Immunology,* 57**,** 44-51.

COMPSTON, J. 2009. Monitoring bone mineral density during antiresorptive treatment for osteoporosis. *BMJ,* 338**,** b1276.

COMPSTON, J. E., MCCLUNG, M. R. & LESLIE, W. D. 2019. Osteoporosis. *Lancet,* 393**,** 364-376.

COOPER, D. M., KAWALILAK, C. E., HARRISON, K., JOHNSTON, B. D. & JOHNSTON, J. D. 2016. Cortical Bone Porosity: What Is It, Why Is It Important, and How Can We Detect It? *Curr Osteoporos Rep,* 14**,** 187-98.

CORTES, A., HADLER, J., POINTON, J. P., ROBINSON, P. C., KARADERI, T., LEO, P., CREMIN, K., PRYCE, K., HARRIS, J., LEE, S., JOO, K. B., SHIM, S. C., WEISMAN, M., WARD, M., ZHOU, X., GARCHON, H. J., CHIOCCHIA, G., NOSSENT, J., LIE, B. A., FORRE, O., TUOMILEHTO, J., LAIHO, K., JIANG, L., LIU, Y., WU, X., BRADBURY, L. A., ELEWAUT, D., BURGOS-VARGAS, R., STEBBINGS, S., APPLETON, L., FARRAH, C., LAU, J., KENNA, T. J., HAROON, N., FERREIRA, M. A., YANG, J., MULERO, J., FERNANDEZ-SUEIRO, J. L., GONZALEZ-GAY, M. A., LOPEZ-LARREA, C., DELOUKAS, P., DONNELLY, P., BOWNESS, P., GAFNEY, K., GASTON, H., GLADMAN, D. D., RAHMAN, P., MAKSYMOWYCH, W. P., XU, H., CRUSIUS, J. B., VAN DER HORST-BRUINSMA, I. E., CHOU, C. T., VALLE-ONATE, R., ROMERO-SANCHEZ, C., HANSEN, I. M., PIMENTEL-SANTOS, F. M., INMAN, R. D., VIDEM, V., MARTIN, J., BREBAN, M., REVEILLE, J. D., EVANS, D. M., KIM, T. H., WORDSWORTH, B. P. & BROWN, M. A. 2013. Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. *Nature Genetics,* 45**,** 730-8.

CORTET, B., BOUTRY, N., DUBOIS, P., LEGROUX-GEROT, I., COTTEN, A. & MARCHANDISE, X. 2004. Does quantitative ultrasound of bone reflect more bone mineral density than bone microarchitecture? *Calcified Tissue International,* 74**,** 60-7.

COSMAN, F., CRITTENDEN, D. B., ADACHI, J. D., BINKLEY, N., CZERWINSKI, E., FERRARI, S., HOFBAUER, L. C., LAU, E., LEWIECKI, E. M., MIYAUCHI, A., ZERBINI, C. A., MILMONT, C. E., CHEN, L., MADDOX, J., MEISNER, P. D., LIBANATI, C. & GRAUER, A. 2016. Romosozumab Treatment in Postmenopausal Women with Osteoporosis. *New England Journal of Medicine,* 375**,** 1532-1543.

COSMAN, F., DE BEUR, S. J., LEBOFF, M. S., LEWIECKI, E. M., TANNER, B., RANDALL, S. & LINDSAY, R. 2014. Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporosis International,* 25**,** 2359-2381.

CRAMER, J. A., GOLD, D. T., SILVERMAN, S. L. & LEWIECKI, E. M. 2007. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. *Osteoporosis International,* 18**,** 1023-31.

CREAMER, P., COATES, L., BHALLA, A., PACKHAM, J., HAILWOOD, S., MULHERIN, D., CHAKRAVARTY, K., MCCLOSKEY, E. V., TAYLOR, G., SHIPLEY, J. & BHALLA, A. K. 2017. Bone density, bone turnover and fracture risk in Ankylosing Spondylitis: a randomized placebo-controlled trial of oral alendronate. *SM Rheumatol,* 1**,** 1001.

CREEMERS, M. C., FRANSSEN, M. J., VAN'T HOF, M. A., GRIBNAU, F. W., VAN DE PUTTE, L. B. & VAN RIEL, P. L. 2005. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. *Annals of the Rheumatic Diseases,* 64**,** 127-9.

CRYER, J. R., OTTER, S. J. & BOWEN, C. J. 2007. Use of quantitative ultrasound scans of the calcaneus to diagnose osteoporosis in patients with rheumatoid arthritis. *Journal of the American Podiatric Medical Association,* 97**,** 108-14.

CUMMINGS, S. R., BLACK, D. M. & RUBIN, S. M. 1989. Lifetime risks of hip, Colles', or vertebral fracture and coronary heart disease among white postmenopausal women. *Archives of Internal Medicine,* 149**,** 2445-8.

CUMMINGS, S. R., BLACK, D. M., THOMPSON, D. E., APPLEGATE, W. B., BARRETT-CONNOR, E., MUSLINER, T. A., PALERMO, L., PRINEAS, R., RUBIN, S. M., SCOTT, J. C., VOGT, T., WALLACE, R., YATES, A. J. & LACROIX, A. Z. 1998. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA,* 280**,** 2077-82.

CUMMINGS, S. R., FERRARI, S., EASTELL, R., GILCHRIST, N., JENSEN, J. B., MCCLUNG, M., ROUX, C., TORRING, O., VALTER, I., WANG, A. T. & BROWN, J. P. 2018. Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension. *Journal of Bone and Mineral Research,* 33**,** 190-198.

CUMMINGS, S. R. & MELTON, L. J. 2002. Epidemiology and outcomes of osteoporotic fractures. *Lancet,* 359**,** 1761-7.

CUMMINGS, S. R., SAN MARTIN, J., MCCLUNG, M. R., SIRIS, E. S., EASTELL, R., REID, I. R., DELMAS, P., ZOOG, H. B., AUSTIN, M., WANG, A., KUTILEK, S., ADAMI, S., ZANCHETTA, J., LIBANATI, C., SIDDHANTI, S. & CHRISTIANSEN, C. 2009. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *New England Journal of Medicine,* 361**,** 756-65.

DANE, C., DANE, B., CETIN, A. & ERGINBAS, M. 2008. The role of quantitative ultrasound in predicting osteoporosis defined by dual-energy X-ray absorptiometry in pre- and postmenopausal women. *Climacteric,* 11**,** 296-303.

DANNINGER, K., HOPPE, U. C. & PIERINGER, H. 2014. Do statins reduce the cardiovascular risk in patients with rheumatoid arthritis? *International Journal of Rheumatic Diseases,* 17**,** 606-11.

DANVE, A. & O'DELL, J. 2015. The ongoing quest for biomarkers in Ankylosing Spondylitis. *International Journal of Rheumatic Diseases,* 18**,** 826-34.

DARUWALLA, Z. J., HUQ, S. S., WONG, K. L., NEE, P. Y., LEONG, K. M., PILLAY, K. R. & MURPHY, D. P. 2016. Hip fractures, preceding distal radius fractures and screening for osteoporosis: should we be screening earlier? A minimum 10-year retrospective cohort study at a single centre. *Osteoporosis International,* 27**,** 361-6.

DAVIS, J. C., VAN DER HEIJDE, D. M., BRAUN, J., DOUGADOS, M., CUSH, J., CLEGG, D., INMAN, R. D., KIVITZ, A., ZHOU, L., SOLINGER, A. & TSUJI, W. 2005. Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. *Annals of the Rheumatic Diseases,* 64**,** 1557-62.

DE WINTER, J. J., VAN MENS, L. J., VAN DER HEIJDE, D., LANDEWE, R. & BAETEN, D. L. 2016. Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-analysis. *Arthritis Research & Therapy,* 18**,** 196.

DEAN, L. E., JONES, G. T., MACDONALD, A. G., DOWNHAM, C., STURROCK, R. D. & MACFARLANE, G. J. 2014. Global prevalence of ankylosing spondylitis. *Rheumatology (Oxford, England),* 53**,** 650-7.
DEL VALLE, H. B., YAKTINE, A. L., TAYLOR, C. L. & ROSS, A. C. 2011. *Dietary reference intakes for calcium and vitamin D*, National Academies Press.

DELAY, M. L., TURNER, M. J., KLENK, E. I., SMITH, J. A., SOWDERS, D. P. & COLBERT, R. A. 2009. HLA-B27 misfolding and the unfolded protein response augment interleukin-23 production and are associated with Th17 activation in transgenic rats. *Arthritis and Rheumatism,* 60**,** 2633-43.

DEMINGER, A., KLINGBERG, E., LORENTZON, M., GEIJER, M., GOTHLIN, J., HEDBERG, M., REHNBERG, E., CARLSTEN, H., JACOBSSON, L. T. & FORSBLAD-D'ELIA, H. 2017. Which measuring site in ankylosing spondylitis is best to detect bone loss and what predicts the decline: results from a 5-year prospective study. *Arthritis Research & Therapy,* 19**,** 273.

DEVLIN, R. D., REDDY, S. V., SAVINO, R., CILIBERTO, G. & ROODMAN, G. D. 1998. IL-6 mediates the effects of IL-1 or TNF, but not PTHrP or 1,25(OH)2D3, on osteoclast-like cell formation in normal human bone marrow cultures. *Journal of Bone and Mineral Research,* 13**,** 393-9.

DEVOGELAER, J. P., MALDAGUE, B., MALGHEM, J. & NAGANT DE DEUXCHAISNES, C. 1992. Appendicular and vertebral bone mass in ankylosing spondylitis. A comparison of plain radiographs with single- and dual-photon absorptiometry and with quantitative computed tomography. *Arthritis and Rheumatism,* 35**,** 1062-7.

DIEDERICHS, C., BERGER, K. & BARTELS, D. B. 2011. The measurement of multiple chronic diseases--a systematic review on existing multimorbidity indices. *Journals of Gerontology. Series A: Biological Sciences and Medical Sciences,* 66**,** 301-11.

DIEZ-PEREZ, A., NAYLOR, K. E., ABRAHAMSEN, B., AGNUSDEI, D., BRANDI, M. L., COOPER, C., DENNISON, E., ERIKSEN, E. F., GOLD, D. T., GUANABENS, N., HADJI, P., HILIGSMANN, M., HORNE, R., JOSSE, R., KANIS, J. A., OBERMAYER-PIETSCH, B., PRIETO-ALHAMBRA, D., REGINSTER, J. Y., RIZZOLI, R., SILVERMAN, S., ZILLIKENS, M. C. & EASTELL, R. 2017. International Osteoporosis Foundation and European Calcified Tissue Society Working Group. Recommendations for the screening of adherence to oral bisphosphonates. *Osteoporosis International,* 28**,** 767-774.

DING, J., GHALI, O., LENCEL, P., BROUX, O., CHAUVEAU, C., DEVEDJIAN, J. C., HARDOUIN, P. & MAGNE, D. 2009. TNF-alpha and IL-1beta inhibit RUNX2 and collagen expression but increase alkaline phosphatase activity and mineralization in human mesenchymal stem cells. *Life Sciences,* 84**,** 499-504.

DODDS, M. K., CODD, M. B., LOONEY, A. & MULHALL, K. J. 2009. Incidence of hip fracture in the Republic of Ireland and future projections: a population-based study. *Osteoporosis International,* 20**,** 2105-10.

DONNELLY, S., DOYLE, D. V., DENTON, A., ROLFE, I., MCCLOSKEY, E. V. & SPECTOR, T. D. 1994. Bone mineral density and vertebral compression fracture rates in ankylosing spondylitis. *Annals of the Rheumatic Diseases,* 53**,** 117-21.

DOUGADOS, M. & BAETEN, D. 2011. Spondyloarthritis. *Lancet,* 377**,** 2127-37.

DOUGADOS, M., ETCHETO, A., MOLTO, A., ALONSO, S., BOUVET, S., DAURES, J. P., LANDAIS, P., D'AGOSTINO, M. A., BERENBAUM, F., BREBAN, M., CLAUDEPIERRE, P., COMBE, B., FAUTREL, B., FEYDY, A., GOUPILLE, P., RICHETTE, P., PHAM, T., ROUX, C., TRELUYER, J. M., SARAUX, A., VAN DER

HEIJDE, D. & WENDLING, D. 2015. Clinical presentation of patients suffering from recent onset chronic inflammatory back pain suggestive of spondyloarthritis: The DESIR cohort. *Joint, Bone, Spine: Revue du Rhumatisme,* 82**,** 345-51.

DOUGADOS, M., VAN DER LINDEN, S., JUHLIN, R., HUITFELDT, B., AMOR, B., CALIN, A., CATS, A., DIJKMANS, B., OLIVIERI, I., PASERO, G. & ET AL. 1991. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis and Rheumatism,* 34**,** 1218-27.

DOWARD, L. C., SPOORENBERG, A., COOK, S. A., WHALLEY, D., HELLIWELL, P. S., KAY, L. J., MCKENNA, S. P., TENNANT, A., VAN DER HEIJDE, D. & CHAMBERLAIN, M. A. 2003. Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. *Annals of the Rheumatic Diseases,* 62**,** 20-6.

DUFFIELD, S. J., ELLIS, B. M., GOODSON, N., WALKER-BONE, K., CONAGHAN, P. G., MARGHAM, T. & LOFTIS, T. 2017. The contribution of musculoskeletal disorders in multimorbidity: Implications for practice and policy. *Best Practice & Research: Clinical Rheumatology,* 31**,** 129-144.

DYER, S. M., CROTTY, M., FAIRHALL, N., MAGAZINER, J., BEAUPRE, L. A., CAMERON, I. D. & SHERRINGTON, C. 2016. A critical review of the long-term disability outcomes following hip fracture. *BMC Geriatrics,* 16**,** 158.

EASTELL, R., PIGOTT, T., GOSSIEL, F., NAYLOR, K. E., WALSH, J. S. & PEEL, N. F. A. 2018. DIAGNOSIS OF ENDOCRINE DISEASE: Bone turnover markers: are they clinically useful? *European Journal of Endocrinology of the European Federation of Endocrine Societies,* 178**,** R19-r31.

EL MAGHRAOUI, A. & DEHHAOUI, M. 2012. Prevalence and characteristics of lung involvement on high resolution computed tomography in patients with ankylosing spondylitis: a systematic review. *Pulmonary Medicine,* 2012**,** 965956.

EL MAGHRAOUI, A., TELLAL, S., CHAOUIR, S., LEBBAR, K., BEZZA, A., NOUIJAI, A., ACHEMLAL, L., BOUHSSAIN, S. & DEROUICHE EL, M. 2005. Bone turnover markers, anterior pituitary and gonadal hormones, and bone mass evaluation using quantitative computed tomography in ankylosing spondylitis. *Clinical Rheumatology,* 24**,** 346-51.

ELLINGHAUS, D., JOSTINS, L., SPAIN, S. L., CORTES, A., BETHUNE, J., HAN, B., PARK, Y. R., RAYCHAUDHURI, S., POUGET, J. G., HUBENTHAL, M., FOLSERAAS, T., WANG, Y., ESKO, T., METSPALU, A., WESTRA, H. J., FRANKE, L., PERS, T. H., WEERSMA, R. K., COLLIJ, V., D'AMATO, M., HALFVARSON, J., JENSEN, A. B., LIEB, W., DEGENHARDT, F., FORSTNER, A. J., HOFMANN, A., SCHREIBER, S., MROWIETZ, U., JURAN, B. D., LAZARIDIS, K. N., BRUNAK, S., DALE, A. M., TREMBATH, R. C., WEIDINGER, S., WEICHENTHAL, M., ELLINGHAUS, E., ELDER, J. T., BARKER, J. N., ANDREASSEN, O. A., MCGOVERN, D. P., KARLSEN, T. H., BARRETT, J. C., PARKES, M., BROWN, M. A. & FRANKE, A. 2016. Analysis of five chronic inflammatory diseases identifies 27 new associations and highlights disease-specific patterns at shared loci. *Nature Genetics,* 48**,** 510-8.

ENSRUD, K. E., BLACKWELL, T. L., FINK, H. A., ZHANG, J., CAULEY, J. A., CAWTHON, P. M., BLACK, D. M., BAUER, D. C., CURTIS, J. R., ORWOLL, E. S., BARRETT-CONNOR, E., KADO, D. M., MARSHALL, L. M., SHIKANY, J. M. & SCHOUSBOE, J. T. 2016. What Proportion of Incident Radiographic Vertebral Fractures

in Older Men Is Clinically Diagnosed and Vice Versa: A Prospective Study. *Journal of Bone and Mineral Research,* 31**,** 1500-3.

ERIKSEN, E. F., DIEZ-PEREZ, A. & BOONEN, S. 2014. Update on long-term treatment with bisphosphonates for postmenopausal osteoporosis: a systematic review. *Bone,* 58**,** 126-35.

ESSOUMA, M. & NOUBIAP, J. J. 2017. Are Systematic Screening for Vitamin D Deficiency and Vitamin D Supplementation Currently Feasible for Ankylosing Spondylitis Patients? *Int J Inflam,* 2017**,** 7840150.

EUROPEAN COMMISSION 2018. The 2018 Ageing Report: Economic and Budgetary Projections for the 28 EU Member States (2016-2070). Brussels.

EXARCHOU, S., LIE, E., LINDSTROM, U., ASKLING, J., FORSBLAD-D'ELIA, H., TURESSON, C., KRISTENSEN, L. E. & JACOBSSON, L. T. 2016. Mortality in ankylosing spondylitis: results from a nationwide population-based study. *Annals of the Rheumatic Diseases,* 75**,** 1466-72.

EXARCHOU, S., LINDSTROM, U., ASKLING, J., ERIKSSON, J. K., FORSBLAD-D'ELIA, H., NEOVIUS, M., TURESSON, C., KRISTENSEN, L. E. & JACOBSSON, L. T. 2015. The prevalence of clinically diagnosed ankylosing spondylitis and its clinical manifestations: a nationwide register study. *Arthritis Research & Therapy,* 17**,** 118.

FEINSTEIN, A. R. 1970. The pre-therapeutic classification of co-morbidity in chronic disease. *Journal of Chronic Diseases,* 23**,** 455-68.

FELTELIUS, N., EKBOM, A. & BLOMQVIST, P. 2003. Cancer incidence among patients with ankylosing spondylitis in Sweden 1965-95: a population based cohort study. *Annals of the Rheumatic Diseases,* 62**,** 1185-8.

FERNANDEZ-ESPARTERO, C., DE MIGUEL, E., LOZA, E., TOMERO, E., GOBBO, M., DESCALZO, M. A., COLLANTES-ESTEVEZ, E., MULERO, J., MUNOZ-FERNANDEZ, S., ZARCO, P. & CARMONA, L. 2014. Validity of the ankylosing spondylitis disease activity score (ASDAS) in patients with early spondyloarthritis from the Esperanza programme. *Annals of the Rheumatic Diseases,* 73**,** 1350-5.

FINK, H. A., MILAVETZ, D. L., PALERMO, L., NEVITT, M. C., CAULEY, J. A., GENANT, H. K., BLACK, D. M. & ENSRUD, K. E. 2005. What proportion of incident radiographic vertebral deformities is clinically diagnosed and vice versa? *Journal of Bone and Mineral Research,* 20**,** 1216-22.

FINKELSTEIN, J. S., CLEARY, R. L., BUTLER, J. P., ANTONELLI, R., MITLAK, B. H., DERASKA, D. J., ZAMORA-QUEZADA, J. C. & NEER, R. M. 1994. A comparison of lateral versus anterior-posterior spine dual energy x-ray absorptiometry for the diagnosis of osteopenia. *The Journal of Clinical Endocrinology & Metabolism,* 78**,** 724-730.

FITZGERALD, G. E. & O'SHEA, F. D. 2017. The Fascinating Paradox of Osteoporosis in Axial Spondyloarthropathy. *The Journal of rheumatology,* 44**,** 1767-1776.

FLEGAL, K. M., KIT, B. K., ORPANA, H. & GRAUBARD, B. I. 2013. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA,* 309**,** 71-82.

FORIEN, M., MOLTO, A., ETCHETO, A., DOUGADOS, M., ROUX, C. & BRIOT, K. 2015. Bone mineral density in patients with symptoms suggestive of spondyloarthritis. *Osteoporosis International,* 26**,** 1647-53.

FOUQUE-AUBERT, A., JETTE-PAULIN, L., COMBESCURE, C., BASCH, A., TEBIB, J. & GOSSEC, L. 2010. Serious infections in patients with ankylosing spondylitis with and without TNF blockers: a systematic review and meta-analysis of randomised placebo-controlled trials. *Annals of the Rheumatic Diseases,* 69**,** 1756-61.

FRANCK, H., MEURER, T. & HOFBAUER, L. C. 2004. Evaluation of bone mineral density, hormones, biochemical markers of bone metabolism, and osteoprotegerin serum levels in patients with ankylosing spondylitis. *Journal of Rheumatology,* 31**,** 2236-41.

FRANKENBERGER, B., BREITKOPF, S., ALBERT, E., SCHOLZ, S., KELLER, E., SCHATTENKIRCHNER, M., WEISS, E. H. & KELLNER, H. 1997. Routine molecular genotyping of HLA-B27 in spondyloarthropathies overcomes the obstacles of serological typing and reveals an increased B *2702 frequency in ankylosing spondylitis. *Journal of Rheumatology,* 24**,** 899-903.

FRIES, J. F. 1983. The compression of morbidity. *Milbank Memorial Fund Quarterly: Health and Society,* 61**,** 397-419.

FRIES, J. F., SPITZ, P., KRAINES, R. G. & HOLMAN, H. R. 1980. Measurement of patient outcome in arthritis. *Arthritis and Rheumatism,* 23**,** 137-45.

FROST, H. M. 1969. Tetracycline-based histological analysis of bone remodeling. *Calcified Tissue Research,* 3**,** 211-37.

FROST, H. M. 1990a. Skeletal structural adaptations to mechanical usage (SATMU): 1. Redefining Wolff's law: the bone modeling problem. *Anatomical Record,* 226**,** 403-13.

FROST, H. M. 1990b. Skeletal structural adaptations to mechanical usage (SATMU): 2. Redefining Wolff's law: the remodeling problem. *Anatomical Record,* 226**,** 414-22.

GAMEZ-NAVA, J. I., DE LA CERDA-TRUJILLO, L. F., VAZQUEZ-VILLEGAS, M. L., CONS-MOLINA, F., ALCARAZ-LOPEZ, M. F., ZAVALETA-MUNIZ, S. A., ROCHA-MUNOZ, A. D., MARTINEZ-GARCIA, E. A., CORONA-SANCHEZ, E. G., SALAZAR-PARAMO, M., FAJARDO-ROBLEDO, N. S., OLIVAS-FLORES, E. M., CARDONA-MUNOZ, E. G. & GONZALEZ-LOPEZ, L. 2016. Association between bone turnover markers, clinical variables, spinal syndesmophytes and bone mineral density in Mexican patients with ankylosing spondylitis. *Scandinavian Journal of Rheumatology,* 45**,** 480-490.

GARRETT, S., JENKINSON, T., KENNEDY, L. G., WHITELOCK, H., GAISFORD, P. & CALIN, A. 1994. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *Journal of Rheumatology,* 21**,** 2286-91.

GAUR, T., LENGNER, C. J., HOVHANNISYAN, H., BHAT, R. A., BODINE, P. V., KOMM, B. S., JAVED, A., VAN WIJNEN, A. J., STEIN, J. L., STEIN, G. S. & LIAN, J. B. 2005. Canonical WNT signaling promotes osteogenesis by directly stimulating Runx2 gene expression. *Journal of Biological Chemistry,* 280**,** 33132-40.

GBD 2013 DALYS AND HALE COLLABORATORS 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and

injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet,* 392**,** 1789-1858.

http://www3.gehealthcare.com.au/~/media/documents/us-global/products/bone-health/abstracts/quantitative%20ultrasound/achilles/gehealthcare-achilles-insight-productspec.pdfGE HEALTHCARE. 2011. *Achilles InSight product data sheet* [Online]. Available: http://www3.gehealthcare.com.au/~/media/documents/us-global/products/bone-health/abstracts/quantitative%20ultrasound/achilles/gehealthcare-achilles-insight-productspec.pdf [Accessed 23 Nov 2017].

GEUSENS, P., DE WINTER, L., QUADEN, D., VANHOOF, J., VOSSE, D., VAN DEN BERGH, J. & SOMERS, V. 2015. The prevalence of vertebral fractures in spondyloarthritis: relation to disease characteristics, bone mineral density, syndesmophytes and history of back pain and trauma. *Arthritis Research & Therapy,* 17.

GHOZLANI, I., GHAZI, M., NOUIJAI, A., MOUNACH, A., REZQI, A., ACHEMLAL, L., BEZZA, A. & EL MAGHRAOUI, A. 2009. Prevalence and risk factors of osteoporosis and vertebral fractures in patients with ankylosing spondylitis. *Bone,* 44**,** 772-6.

GILBERT, L., HE, X., FARMER, P., RUBIN, J., DRISSI, H., VAN WIJNEN, A. J., LIAN, J. B., STEIN, G. S. & NANES, M. S. 2002. Expression of the osteoblast differentiation factor RUNX2 (Cbfa1/AML3/Pebp2alpha A) is inhibited by tumor necrosis factor-alpha. *Journal of Biological Chemistry,* 277**,** 2695-701.

GILLESPIE, L. D., ROBERTSON, M. C., GILLESPIE, W. J., SHERRINGTON, C., GATES, S., CLEMSON, L. M. & LAMB, S. E. 2012. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev***,** Cd007146.

GILSENAN, A., HARDING, A., KELLIER-STEELE, N., HARRIS, D., MIDKIFF, K. & ANDREWS, E. 2018. The Forteo Patient Registry linkage to multiple state cancer registries: study design and results from the first 8 years. *Osteoporosis International,* 29**,** 2335-2343.

GILTAY, E. J., POPP-SNIJDERS, C., VAN SCHAARDENBURG, D., DEKKER-SAEYS, B. J., GOOREN, L. J. & DIJKMANS, B. A. 1998. Serum testosterone levels are not elevated in patients with ankylosing spondylitis. *Journal of Rheumatology,* 25**,** 2389-94.

GILTAY, E. J., VAN SCHAARDENBURG, D., GOOREN, L. J., POPP-SNIJDERS, C. & DIJKMANS, B. A. 1999. Androgens and ankylosing spondylitis: a role in the pathogenesis? *Annals of the New York Academy of Sciences,* 876**,** 340-64; discussion 365.

GLINTBORG, B., SORENSEN, I. J., OSTERGAARD, M., DREYER, L., MOHAMOUD, A. A., KROGH, N. S., HENDRICKS, O., ANDERSEN, L. S., RAUN, J. L., KOWALSKI, M. R., DANIELSEN, L., PELCK, R., NORDIN, H., PEDERSEN, J. K., KRAUS, D. G., CHRISTENSEN, S. R., HANSEN, I. M., ESBESEN, J., SCHLEMMER, A., LOFT, A. G., AL CHAER, N., SALOMONSEN, L. & HETLAND, M. L. 2017. Ankylosing Spondylitis versus Nonradiographic Axial Spondyloarthritis: Comparison of Tumor Necrosis Factor Inhibitor Effectiveness and Effect of HLA-B27 Status. An Observational Cohort Study from the Nationwide DANBIO Registry. *Journal of Rheumatology,* 44**,** 59-69.

GOLDRING, S. R. 2013. Osteoimmunology and bone homeostasis: relevance to spondyloarthritis. *Current Rheumatology Reports,* 15**,** 342.

GOLDRING, S. R., PURDUE, P. E., CROTTI, T. N., SHEN, Z., FLANNERY, M. R., BINDER, N. B., ROSS, F. P. & MCHUGH, K. P. 2013. Bone remodelling in inflammatory arthritis. *Annals of the Rheumatic Diseases,* 72 Suppl 2**,** ii52-5.

GONNELLI, S., CEPOLLARO, C., GENNARI, L., MONTAGNANI, A., CAFFARELLI, C., MERLOTTI, D., ROSSI, S., CADIRNI, A. & NUTI, R. 2005. Quantitative ultrasound and dual-energy X-ray absorptiometry in the prediction of fragility fracture in men. *Osteoporosis International,* 16**,** 963-8.

GRAN, J. T., MELLBY, A. S. & HUSBY, G. 1984. The prevalence of HLA-B27 in Northern Norway. *Scandinavian Journal of Rheumatology,* 13**,** 173-6.

GRATACOS, J., COLLADO, A., PONS, F., OSABA, M., SANMARTI, R., ROQUE, M., LARROSA, M. & MUNOZ-GOMEZ, J. 1999. Significant loss of bone mass in patients with early, active ankylosing spondylitis: a followup study. *Arthritis and Rheumatism,* 42**,** 2319-24.

GRAZIO, S., KUSIC, Z., CVIJETIC, S., GRUBISIC, F., BALENOVIC, A., NEMCIC, T., MATIJEVIC-MIKELIC, V., PUNDA, M. & SIEPER, J. 2012. Relationship of bone mineral density with disease activity and functional ability in patients with ankylosing spondylitis: a cross-sectional study. *Rheumatology International,* 32**,** 2801-8.

GREENBLATT, M. B., TSAI, J. N. & WEIN, M. N. 2017. Bone Turnover Markers in the Diagnosis and Monitoring of Metabolic Bone Disease. *Clinical Chemistry,* 63**,** 464-474.

GUGLIELMI, G. & DE TERLIZZI, F. 2009. Quantitative ultrasond in the assessment of osteoporosis. *European Journal of Radiology,* 71**,** 425-31.

GULA, Z., KOPCZYNSKA, A., HANSKA, K., SLOMSKI, M., NOWAKOWSKI, J., KWASNY-KROCHIN, B., GASOWSKI, J. & KORKOSZ, M. 2018. Vitamin D serum concentration is not related to the activity of spondyloarthritis - preliminary study. *Reumatologia,* 56**,** 388-391.

HAENTJENS, P., MAGAZINER, J., COLON-EMERIC, C. S., VANDERSCHUEREN, D., MILISEN, K., VELKENIERS, B. & BOONEN, S. 2010. Meta-analysis: excess mortality after hip fracture among older women and men. *Annals of Internal Medicine,* 152**,** 380-90.

HAGEN, K. B., DAGFINRUD, H., MOE, R. H., OSTERAS, N., KJEKEN, I., GROTLE, M. & SMEDSLUND, G. 2012. Exercise therapy for bone and muscle health: an overview of systematic reviews. *BMC Medicine,* 10**,** 167.

HAGINO, H. 2013. Other non-vertebral fractures. *Best Practice & Research: Clinical Rheumatology,* 27**,** 731-41.

HAMILTON, L., MACGREGOR, A., WARMINGTON, V., PINCH, E. & GAFFNEY, K. 2014. The prevalence of inflammatory back pain in a UK primary care population. *Rheumatology (Oxford, England),* 53**,** 161-4.

HAMMER, R. E., MAIKA, S. D., RICHARDSON, J. A., TANG, J. P. & TAUROG, J. D. 1990. Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human beta 2m: an animal model of HLA-B27-associated human disorders. *Cell,* 63**,** 1099-112.

HANLON, P., NICHOLL, B. I., JANI, B. D., LEE, D., MCQUEENIE, R. & MAIR, F. S. 2018. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. *Lancet Public Health,* 3**,** e323-e332.

HANS, D., BARTHE, N., BOUTROY, S., POTHUAUD, L., WINZENRIETH, R. & KRIEG, M. A. 2011a. Correlations between trabecular bone score, measured using anteroposterior dual-energy X-ray absorptiometry acquisition, and 3-dimensional parameters of bone microarchitecture: an experimental study on human cadaver vertebrae. *Journal of Clinical Densitometry,* 14**,** 302-12.

HANS, D., GOERTZEN, A. L., KRIEG, M. A. & LESLIE, W. D. 2011b. Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: the Manitoba study. *Journal of Bone and Mineral Research,* 26**,** 2762-9.

HANS, D., WU, C., NJEH, C. F., ZHAO, S., AUGAT, P., NEWITT, D., LINK, T., LU, Y., MAJUMDAR, S. & GENANT, H. K. 1999. Ultrasound velocity of trabecular cubes reflects mainly bone density and elasticity. *Calcified Tissue International,* 64**,** 18-23.

HANSEN, L., PETERSEN, K. D., ERIKSEN, S. A., LANGDAHL, B. L., EIKEN, P. A., BRIXEN, K., ABRAHAMSEN, B., JENSEN, J. E., HARSLOF, T. & VESTERGAARD, P. 2015. Subsequent fracture rates in a nationwide population-based cohort study with a 10-year perspective. *Osteoporosis International,* 26**,** 513-9.

HAROON, N. N., PATERSON, J. M., LI, P., INMAN, R. D. & HAROON, N. 2015. Patients With Ankylosing Spondylitis Have Increased Cardiovascular and Cerebrovascular Mortality: A Population-Based Study. *Annals of Internal Medicine,* 163**,** 409-16.

HAROON, N. N., SRIGANTHAN, J., AL GHANIM, N., INMAN, R. D. & CHEUNG, A. M. 2014. Effect of TNF-alpha inhibitor treatment on bone mineral density in patients with ankylosing spondylitis: a systematic review and meta-analysis. *Seminars in Arthritis and Rheumatism,* 44**,** 155-61.

HARRE, U., GEORGESS, D., BANG, H., BOZEC, A., AXMANN, R., OSSIPOVA, E., JAKOBSSON, P. J., BAUM, W., NIMMERJAHN, F., SZARKA, E., SARMAY, G., KRUMBHOLZ, G., NEUMANN, E., TOES, R., SCHERER, H. U., CATRINA, A. I., KLARESKOG, L., JURDIC, P. & SCHETT, G. 2012. Induction of osteoclastogenesis and bone loss by human autoantibodies against citrullinated vimentin. *Journal of Clinical Investigation,* 122**,** 1791-802.

HARRIS, S. T., WATTS, N. B., GENANT, H. K., MCKEEVER, C. D., HANGARTNER, T., KELLER, M., CHESNUT III, C. H., BROWN, J., ERIKSEN, E. F., HOSEYNI, M. S., AXELROD, D. W., MILLER, P. D. & GROUP, F. T. V. E. W. R. T. S. 1999. Effects of Risedronate Treatment on Vertebral and Nonvertebral Fractures in Women With Postmenopausal OsteoporosisA Randomized Controlled Trial. *JAMA,* 282**,** 1344-1352.

HART, F. D. 1948. Ankylosing spondylitis. *Lancet,* 1**,** 84.

HARVEY, N. C., GLUER, C. C., BINKLEY, N., MCCLOSKEY, E. V., BRANDI, M. L., COOPER, C., KENDLER, D., LAMY, O., LASLOP, A., CAMARGOS, B. M., REGINSTER, J. Y., RIZZOLI, R. & KANIS, J. A. 2015. Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice. *Bone,* 78**,** 216-24.

HATTNER, R., EPKER, B. N. & FROST, H. M. 1965. Suggested sequential mode of control of changes in cell behaviour in adult bone remodelling. *Nature,* 206**,** 489-90.
HAUGER, A. V., BERGLAND, A., HOLVIK, K., STAHLE, A., EMAUS, N. & STRAND, B. H. 2018. Osteoporosis and osteopenia in the distal forearm predict all-cause mortality independent of grip strength: 22-year follow-up in the population-based Tromso Study. *Osteoporosis International,* 29**,** 2447-2456.

HAUSER, B., RICHES, P. L., WILSON, J. F., HORNE, A. E. & RALSTON, S. H. 2014. Prevalence and clinical prediction of osteoporosis in a contemporary cohort of patients with rheumatoid arthritis. *Rheumatology (Oxford, England),* 53**,** 1759-66.

HAYEN, A., MACASKILL, P., IRWIG, L. & BOSSUYT, P. 2010. Appropriate statistical methods are required to assess diagnostic tests for replacement, add-on, and triage. *Journal of Clinical Epidemiology,* 63**,** 883-91.

HAYWOOD, K. L., A, M. G., JORDAN, K., DZIEDZIC, K. & DAWES, P. T. 2002. Disease-specific, patient-assessed measures of health outcome in ankylosing spondylitis: reliability, validity and responsiveness. *Rheumatology (Oxford, England),* 41**,** 1295-302.

https://www.hse.ie/eng/health/hl/change/alcohol/HEALTH SERVICE EXECUTIVE. 2015. *Alcohol Programme* [Online]. Available: https://www.hse.ie/eng/health/hl/change/alcohol/ [Accessed 12 Nov 2018].

HENDRICKX, G., BOUDIN, E. & VAN HUL, W. 2015. A look behind the scenes: the risk and pathogenesis of primary osteoporosis. *Nature Reviews: Rheumatology,* 11**,** 462-74.

HERMANN, K. G., BARALIAKOS, X., VAN DER HEIJDE, D. M., JURIK, A. G., LANDEWE, R., MARZO-ORTEGA, H., OSTERGAARD, M., RUDWALEIT, M., SIEPER, J. & BRAUN, J. 2012. Descriptions of spinal MRI lesions and definition of a positive MRI of the spine in axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI study group. *Annals of the Rheumatic Diseases,* 71**,** 1278-88.

HERNLUND, E., SVEDBOM, A., IVERGARD, M., COMPSTON, J., COOPER, C., STENMARK, J., MCCLOSKEY, E. V., JONSSON, B. & KANIS, J. A. 2013. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch Osteoporos,* 8**,** 136.

HEUFT-DORENBOSCH, L., VAN TUBERGEN, A., SPOORENBERG, A., LANDEWE, R., DOUGADOS, M., MIELANTS, H., VAN DER TEMPEL, H. & VAN DER HEIJDE, D. 2004. The influence of peripheral arthritis on disease activity in ankylosing spondylitis patients as measured with the Bath Ankylosing Spondylitis Disease Activity Index. *Arthritis and Rheumatism,* 51**,** 154-9.

HIGGINS, J., STERNE, J., SAVOVIC, J., PAGE, M., HROBJARTSSON, A., BOUTRON, I., REEVES, B. & ELDRIDGE, S. 2016. A revised tool for assessing risk of bias in randomized trials. *Cochrane Database of Systematic Reviews*.

HOPEWELL, S., ADEDIRE, O., COPSEY, B. J., BONIFACE, G. J., SHERRINGTON, C., CLEMSON, L., CLOSE, J. C. & LAMB, S. E. 2018. Multifactorial and multiple component interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev,* 7**,** Cd012221.

HOWE, T. E., SHEA, B., DAWSON, L. J., DOWNIE, F., MURRAY, A., ROSS, C., HARBOUR, R. T., CALDWELL, L. M. & CREED, G. 2011. *Cochrane Database Syst Rev***,** Cd000333.
HOY, D., BAIN, C., WILLIAMS, G., MARCH, L., BROOKS, P., BLYTH, F., WOOLF, A., VOS, T. & BUCHBINDER, R. 2012. A systematic review of the global prevalence of low back pain. *Arthritis and Rheumatism,* 64**,** 2028-37.

HUBER, A. M. & WARD, L. M. 2016. The impact of underlying disease on fracture risk and bone mineral density in children with rheumatic disorders: A review of current literature. *Seminars in Arthritis and Rheumatism,* 46**,** 49-63.

HUBER, F., TRABER, L., ROTH, H. J., HECKEL, V. & SCHMIDT-GAYK, H. 2003. Markers of bone resorption--measurement in serum, plasma or urine? *Clínica y Laboratorio,* 49**,** 203-7.

HUGHES, F. J. & HOWELLS, G. L. 1993. Interleukin-6 inhibits bone formation in vitro. *Bone and Mineral,* 21**,** 21-8.

HUKUDA, S., MINAMI, M., SAITO, T., MITSUI, H., MATSUI, N., KOMATSUBARA, Y., MAKINO, H., SHIBATA, T., SHINGU, M., SAKOU, T. & SHICHIKAWA, K. 2001. Spondyloarthropathies in Japan: nationwide questionnaire survey performed by the Japan Ankylosing Spondylitis Society. *Journal of Rheumatology,* 28**,** 554-9.

ISIDORI, A. M., GIANNETTA, E., GRECO, E. A., GIANFRILLI, D., BONIFACIO, V., ISIDORI, A., LENZI, A. & FABBRI, A. 2005. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. *Clinical Endocrinology,* 63**,** 280-93.

JACKSON, R. D., LACROIX, A. Z., GASS, M., WALLACE, R. B., ROBBINS, J., LEWIS, C. E., BASSFORD, T., BERESFORD, S. A., BLACK, H. R., BLANCHETTE, P., BONDS, D. E., BRUNNER, R. L., BRZYSKI, R. G., CAAN, B., CAULEY, J. A., CHLEBOWSKI, R. T., CUMMINGS, S. R., GRANEK, I., HAYS, J., HEISS, G., HENDRIX, S. L., HOWARD, B. V., HSIA, J., HUBBELL, F. A., JOHNSON, K. C., JUDD, H., KOTCHEN, J. M., KULLER, L. H., LANGER, R. D., LASSER, N. L., LIMACHER, M. C., LUDLAM, S., MANSON, J. E., MARGOLIS, K. L., MCGOWAN, J., OCKENE, J. K., O'SULLIVAN, M. J., PHILLIPS, L., PRENTICE, R. L., SARTO, G. E., STEFANICK, M. L., VAN HORN, L., WACTAWSKI-WENDE, J., WHITLOCK, E., ANDERSON, G. L., ASSAF, A. R. & BARAD, D. 2006. Calcium plus vitamin D supplementation and the risk of fractures. *New England Journal of Medicine,* 354**,** 669-83.

JACKSON, R. D. & SHIDHAM, S. 2007. The role of hormone therapy and calcium plus vitamin D for reduction of bone loss and risk for fractures: lessons learned from the Women's Health Initiative. *Curr Osteoporos Rep,* 5**,** 153-9.

JACQUES, P., LAMBRECHT, S., VERHEUGEN, E., PAUWELS, E., KOLLIAS, G., ARMAKA, M., VERHOYE, M., VAN DER LINDEN, A., ACHTEN, R., LORIES, R. J. & ELEWAUT, D. 2014. Proof of concept: enthesitis and new bone formation in spondyloarthritis are driven by mechanical strain and stromal cells. *Annals of the Rheumatic Diseases,* 73**,** 437-45.

JALAVA, T., SARNA, S., PYLKKANEN, L., MAWER, B., KANIS, J. A., SELBY, P., DAVIES, M., ADAMS, J., FRANCIS, R. M., ROBINSON, J. & MCCLOSKEY, E.

2003. Association between vertebral fracture and increased mortality in osteoporotic patients. *Journal of Bone and Mineral Research,* 18**,** 1254-60.

JANELE, D., LANG, T., CAPELLINO, S., CUTOLO, M., DA SILVA, J. A. & STRAUB, R. H. 2006. Effects of testosterone, 17beta-estradiol, and downstream estrogens on cytokine secretion from human leukocytes in the presence and absence of cortisol. *Annals of the New York Academy of Sciences,* 1069**,** 168-82.

JANEWAY, C. A., TRAVERS, P., WALPORT, M. & SHLOMCHIK, M. J. 2005. *Immunobiology: the immune system in health and disease,* New York, Garland Publishing.

JANSEN, T. L., AARTS, M. H., ZANEN, S. & BRUYN, G. A. 2003. Risk assessment for osteoporosis by quantitative ultrasound of the heel in ankylosing spondylitis. *Clinical and Experimental Rheumatology,* 21**,** 599-604.

JENKINSON, T. R., MALLORIE, P. A., WHITELOCK, H. C., KENNEDY, L. G., GARRETT, S. L. & CALIN, A. 1994. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. *Journal of Rheumatology,* 21**,** 1694-8.

JIN, S., HSIEH, E., PENG, L., YU, C., WANG, Y., WU, C., WANG, Q., LI, M. & ZENG, X. 2018. Incidence of fractures among patients with rheumatoid arthritis: a systematic review and meta-analysis. *Osteoporosis International,* 29**,** 1263-1275.

JOHANSSON, H., ODEN, A., KANIS, J. A., MCCLOSKEY, E. V., MORRIS, H. A., COOPER, C. & VASIKARAN, S. 2014. A meta-analysis of reference markers of bone turnover for prediction of fracture. *Calcified Tissue International,* 94**,** 560-7.

JOHNELL, O. & KANIS, J. A. 2006. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporosis International,* 17**,** 1726-33.

JOHNSEN, K., GRAN, J. T., DALE, K. & HUSBY, G. 1992. The prevalence of ankylosing spondylitis among Norwegian Samis (Lapps). *Journal of Rheumatology,* 19**,** 1591-4.

JOIS, R. N., MACGREGOR, A. J. & GAFFNEY, K. 2008. Recognition of inflammatory back pain and ankylosing spondylitis in primary care. *Rheumatology (Oxford, England),* 47**,** 1364-6.

JONES, S. D., STEINER, A., GARRETT, S. L. & CALIN, A. 1996. The Bath Ankylosing Spondylitis Patient Global Score (BAS-G). *British Journal of Rheumatology,* 35**,** 66-71.

JOVANI, V., BLASCO-BLASCO, M., RUIZ-CANTERO, M. T. & PASCUAL, E. 2017. Understanding How the Diagnostic Delay of Spondyloarthritis Differs Between Women and Men: A Systematic Review and Metaanalysis. *Journal of Rheumatology,* 44**,** 174-183.

JUN, J. B., JOO, K. B., HER, M. Y., KIM, T. H., BAE, S. C., YOO, D. H. & KIM, S. K. 2006. Femoral bone mineral density is associated with vertebral fractures in patients with ankylosing spondylitis: a cross-sectional study. *Journal of Rheumatology,* 33**,** 1637-41.

JUNJIE, W., DONGSHENG, H., LEI, S., HONGZHUO, L. & CHANGYING, S. 2019. Testosterone Replacement Therapy Has Limited Effect on Increasing Bone Mass Density in Older Men: a Meta-analysis. *Current Pharmaceutical Design,* 25**,** 73-84.

KAELEY, G. S., EDER, L., AYDIN, S. Z., GUTIERREZ, M. & BAKEWELL, C. 2018. Dactylitis: A hallmark of psoriatic arthritis. *Seminars in Arthritis and Rheumatism,* 48**,** 263-273.

KANG, K. Y., HONG, Y. S., PARK, S. H. & JU, J. H. 2015. Low levels of serum uric Acid increase the risk of low bone mineral density in young male patients with ankylosing spondylitis. *Journal of Rheumatology,* 42**,** 968-74.

KANG, K. Y., JU, J. H., PARK, S. H. & KIM, H. Y. 2013. The paradoxical effects of TNF inhibitors on bone mineral density and radiographic progression in patients with ankylosing spondylitis. *Rheumatology (Oxford, England),* 52**,** 718-26.

KANG, K. Y., KIM, I. J., PARK, S. H. & HONG, Y. S. 2018. Associations between trabecular bone score and vertebral fractures in patients with axial spondyloarthritis. *Rheumatology (Oxford, England),* 57**,** 1033-1040.

KANIS, J. A. 2002. Diagnosis of osteoporosis and assessment of fracture risk. *Lancet,* 359**,** 1929-36.

KANIS, J. A., MCCLOSKEY, E. V., JOHANSSON, H., ODEN, A., MELTON, L. J., 3RD & KHALTAEV, N. 2008. A reference standard for the description of osteoporosis. *Bone,* 42**,** 467-75.

KARBERG, K., ZOCHLING, J., SIEPER, J., FELSENBERG, D. & BRAUN, J. 2005. Bone loss is detected more frequently in patients with ankylosing spondylitis with syndesmophytes. *Journal of Rheumatology,* 32**,** 1290-8.

KATHURIA, P., GORDON, K. B. & SILVERBERG, J. I. 2017. Association of psoriasis and psoriatic arthritis with osteoporosis and pathological fractures. *Journal of the American Academy of Dermatology,* 76**,** 1045-1053.e3.

KATSIMBRI, P. 2017. The biology of normal bone remodelling. *European Journal of Cancer Care (English Language Edition),* 26.

KATSOULIS, M., BENETOU, V., KARAPETYAN, T., FESKANICH, D., GRODSTEIN, F., PETTERSSON-KYMMER, U., ERIKSSON, S., WILSGAARD, T., JORGENSEN, L., AHMED, L. A., SCHOTTKER, B., BRENNER, H., BELLAVIA, A., WOLK, A., KUBINOVA, R., STEGEMAN, B., BOBAK, M., BOFFETTA, P. & TRICHOPOULOU, A. 2017. Excess mortality after hip fracture in elderly persons from Europe and the USA: the CHANCES project. *Journal of Internal Medicine,* 281**,** 300-310.

KEAT, A., BENNETT, A. N., GAFFNEY, K., MARZO-ORTEGA, H., SENGUPTA, R. & EVERISS, T. 2017. Should axial spondyloarthritis without radiographic changes be treated with anti-TNF agents? *Rheumatology International,* 37**,** 327-336.

KEITH, R. C., SOKOLOVE, J., EDELMAN, B. L., LAHEY, L., REDENTE, E. F., HOLERS, V. M., SAKAGUCHI, S., ROBINSON, W. H. & RICHES, D. W. 2013. Testosterone is protective in the sexually dimorphic development of arthritis and lung disease in SKG mice. *Arthritis and Rheumatism,* 65**,** 1487-93.

KELLOGG, E. W., 3RD & FRIDOVICH, I. 1977. Liposome oxidation and erythrocyte lysis by enzymically generated superoxide and hydrogen peroxide. *Journal of Biological Chemistry,* 252**,** 6721-8.

KHABBAZI, A., NOSHAD, H., GAFARZADEH, S., HAJIALILOO, M. & KOLAHI, S. 2014. Alendronate Effect on the Prevention of Bone loss in Early Stages of Ankylosing Spondylitis: A Randomized, Double-Blind, Placebo-Controlled Pilot Study. *Iran Red Crescent Med J,* 16**,** e18022.

KHAN, M. A. 1978. Race-related differences in HLA association with ankylosing spondylitis and Reiter's disease in American blacks and whites. *Journal of the National Medical Association,* 70**,** 41-2.

KHAN, M. A. 1995. HLA-B27 and its subtypes in world populations. *Current Opinion in Rheumatology,* 7**,** 263-9.

KHAN, M. A. 2013. Polymorphism of HLA-B27: 105 subtypes currently known. *Current Rheumatology Reports,* 15**,** 362.

KHAN, M. A., KHAN, M. K. & KUSHNER, I. 1981. Survival among patients with ankylosing spondylitis: a life-table analysis. *Journal of Rheumatology,* 8**,** 86-90.

KILIC, E., KILIC, G., AKGUL, O. & OZGOCMEN, S. 2015. Discriminant validity of the Ankylosing Spondylitis Disease Activity Score (ASDAS) in patients with non-radiographic axial spondyloarthritis and ankylosing spondylitis: a cohort study. *Rheumatology International,* 35**,** 981-9.

KIM, D., CHO, S. K., CHOI, C. B., JUN, J. B., KIM, T. H., LEE, H. S., LEE, J., LEE, S. S., YOO, D. H., YOO, W. H., SUNG, Y. K. & BAE, S. C. 2016. Incidence and risk factors of fractures in patients with rheumatoid arthritis: an Asian prospective cohort study. *Rheumatology International,* 36**,** 1205-14.

KLEYER, A., FINZEL, S., RECH, J., MANGER, B., KRIETER, M., FAUSTINI, F., ARAUJO, E., HUEBER, A. J., HARRE, U., ENGELKE, K. & SCHETT, G. 2014. Bone loss before the clinical onset of rheumatoid arthritis in subjects with anticitrullinated protein antibodies. *Annals of the Rheumatic Diseases,* 73**,** 854-60.

KLINGBERG, E., CARLSTEN, H., HILME, E., HEDBERG, M. & FORSBLAD-D'ELIA, H. 2012a. Calprotectin in ankylosing spondylitis--frequently elevated in feces, but normal in serum. *Scandinavian Journal of Gastroenterology,* 47**,** 435-44.

KLINGBERG, E., GEIJER, M., GOTHLIN, J., MELLSTROM, D., LORENTZON, M., HILME, E., HEDBERG, M., CARLSTEN, H. & FORSBLAD-D'ELIA, H. 2012b. Vertebral fractures in ankylosing spondylitis are associated with lower bone mineral density in both central and peripheral skeleton. *Journal of Rheumatology,* 39**,** 1987-95.

KLINGBERG, E., LORENTZON, M., GOTHLIN, J., MELLSTROM, D., GEIJER, M., OHLSSON, C., ATKINSON, E. J., KHOSLA, S., CARLSTEN, H. & FORSBLAD-D'ELIA, H. 2013. Bone microarchitecture in ankylosing spondylitis and the association with bone mineral density, fractures, and syndesmophytes. *Arthritis Research & Therapy,* 15**,** R179.

KLINGBERG, E., LORENTZON, M., MELLSTROM, D., GEIJER, M., GOTHLIN, J., HILME, E., HEDBERG, M., CARLSTEN, H. & FORSBLAD-D'ELIA, H. 2012c. Osteoporosis in ankylosing spondylitis - prevalence, risk factors and methods of assessment. *Arthritis Research & Therapy,* 14**,** R108.

KLINGBERG, E., OLEROD, G., HAMMARSTEN, O. & FORSBLAD-D'ELIA, H. 2016. The vitamin D status in ankylosing spondylitis in relation to intestinal inflammation, disease activity, and bone health: a cross-sectional study. *Osteoporosis International,* 27**,** 2027-33.

KLINGBERG, E., STRID, H., STAHL, A., DEMINGER, A., CARLSTEN, H., OHMAN, L. & FORSBLAD-D'ELIA, H. 2017. A longitudinal study of fecal calprotectin and the development of inflammatory bowel disease in ankylosing spondylitis. *Arthritis Research & Therapy,* 19**,** 21.

KOBAYASHI, K., TAKAHASHI, N., JIMI, E., UDAGAWA, N., TAKAMI, M., KOTAKE, S., NAKAGAWA, N., KINOSAKI, M., YAMAGUCHI, K., SHIMA, N., YASUDA, H., MORINAGA, T., HIGASHIO, K., MARTIN, T. J. & SUDA, T. 2000. Tumor necrosis factor alpha stimulates osteoclast differentiation by a mechanism independent of the ODF/RANKL-RANK interaction. *Journal of Experimental Medicine,* 191**,** 275-86.

KORKOSZ, M., GASOWSKI, J., GRZANKA, P., GORCZOWSKI, J., PLUSKIEWICZ, W., JEKA, S. & GRODZICKI, T. 2011. Baseline new bone formation does not predict bone loss in ankylosing spondylitis as assessed by quantitative computed tomography (QCT): 10-year follow-up. *BMC Musculoskeletal Disorders,* 12**,** 121.

KROON, F. P., VAN DER BURG, L. R., RAMIRO, S., LANDEWE, R. B., BUCHBINDER, R., FALZON, L. & VAN DER HEIJDE, D. 2015. Non-steroidal anti-inflammatory drugs (NSAIDs) for axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis). *Cochrane Database Syst Rev***,** Cd010952.

KRUM, S. A., CHANG, J., MIRANDA-CARBONI, G. & WANG, C. Y. 2010. Novel functions for NFkappaB: inhibition of bone formation. *Nature Reviews: Rheumatology,* 6**,** 607-11.

KVIATKOVSKY, M. J., RAMIRO, S., LANDEWE, R., DOUGADOS, M., TUBACH, F., BELLAMY, N., HOCHBERG, M., RAVAUD, P., MARTIN-MOLA, E., AWADA, H., BOMBARDIER, C., FELSON, D., HAJJAJ-HASSOUNI, N., LOGEART, I., MATUCCI-CERINIC, M., VAN DE LAAR, M. & VAN DER HEIJDE, D. 2016. The Minimum Clinically Important Improvement and Patient-acceptable Symptom State in the BASDAI and BASFI for Patients with Ankylosing Spondylitis. *Journal of Rheumatology,* 43**,** 1680-6.

KYLE, T. K., DHURANDHAR, E. J. & ALLISON, D. B. 2016. Regarding Obesity as a Disease: Evolving Policies and Their Implications. *Endocrinology and Metabolism Clinics of North America,* 45**,** 511-20.

LAM, J., TAKESHITA, S., BARKER, J. E., KANAGAWA, O., ROSS, F. P. & TEITELBAUM, S. L. 2000. TNF-alpha induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. *Journal of Clinical Investigation,* 106**,** 1481-8.

LAMBERT, R. G., BAKKER, P. A., VAN DER HEIJDE, D., WEBER, U., RUDWALEIT, M., HERMANN, K. G., SIEPER, J., BARALIAKOS, X., BENNETT, A., BRAUN, J., BURGOS-VARGAS, R., DOUGADOS, M., PEDERSEN, S. J., JURIK, A. G., MAKSYMOWYCH, W. P., MARZO-ORTEGA, H., OSTERGAARD, M., PODDUBNYY, D., REIJNIERSE, M., VAN DEN BOSCH, F., VAN DER HORST-BRUINSMA, I. & LANDEWE, R. 2016. Defining active sacroiliitis on MRI for

classification of axial spondyloarthritis: update by the ASAS MRI working group. *Annals of the Rheumatic Diseases,* 75**,** 1958-1963.

LANGE, U., KLUGE, A., STRUNK, J., TEICHMANN, J. & BACHMANN, G. 2005a. Ankylosing spondylitis and bone mineral density--what is the ideal tool for measurement? *Rheumatology International,* 26**,** 115-20.

LANGE, U., TEICHMANN, J., STRUNK, J., MULLER-LADNER, U. & SCHMIDT, K. L. 2005b. Association of 1.25 vitamin D3 deficiency, disease activity and low bone mass in ankylosing spondylitis. *Osteoporosis International,* 16**,** 1999-2004.

LEE, J. H., SUNG, Y. K., CHOI, C. B., CHO, S. K., BANG, S. Y., CHOE, J. Y., HONG, S. J., JUN, J. B., KIM, T. H., LEE, J., LEE, H. S., YOO, D. H., YOON, B. Y. & BAE, S. C. 2016. The frequency of and risk factors for osteoporosis in Korean patients with rheumatoid arthritis. *BMC Musculoskeletal Disorders,* 17**,** 98.

LEE, J. S., OH, B. L., LEE, H. Y., SONG, Y. W. & LEE, E. Y. 2018. Comorbidity, disability, and healthcare expenditure of ankylosing spondylitis in Korea: A population-based study. *PloS One,* 13**,** e0192524.

LEE, S. G., PARK, Y. E., PARK, S. H., KIM, T. K., CHOI, H. J., LEE, S. J., KIM, S. I., LEE, S. H., KIM, G. T., LEE, J. W., LEE, J. H. & BAEK, S. H. 2012. Increased frequency of osteoporosis and BMD below the expected range for age among South Korean women with rheumatoid arthritis. *International Journal of Rheumatic Diseases,* 15**,** 289-96.

LEE, Y. H., JI, J. D., KIM, J. S., BAK, Y. T., LEE, C. H., KIM, C. H., CHAE, Y. S. & SONG, G. G. 1997. Ileocolonoscopic and histologic studies of Korean patients with ankylosing spondylitis. *Scandinavian Journal of Rheumatology,* 26**,** 473-6.

LEHTINEN, K. 1993. Mortality and causes of death in 398 patients admitted to hospital with ankylosing spondylitis. *Annals of the Rheumatic Diseases,* 52**,** 174-6.

LEIRISALO-REPO, M., TURUNEN, U., STENMAN, S., HELENIUS, P. & SEPPALA, K. 1994. High frequency of silent inflammatory bowel disease in spondylarthropathy. *Arthritis and Rheumatism,* 37**,** 23-31.

LESLIE, W. D., PAHLAVAN, P. S., TSANG, J. F. & LIX, L. M. 2009. Prediction of hip and other osteoporotic fractures from hip geometry in a large clinical cohort. *Osteoporosis International,* 20**,** 1767-74.

LI, H., LI, Q., CHEN, X., JI, C. & GU, J. 2015. Anti-tumor Necrosis Factor Therapy Increased Spine and Femoral Neck Bone Mineral Density of Patients with Active Ankylosing Spondylitis with Low Bone Mineral Density. *Journal of Rheumatology,* 42**,** 1413-7.

LIAN, J. B., STEIN, G. S., JAVED, A., VAN WIJNEN, A. J., STEIN, J. L., MONTECINO, M., HASSAN, M. Q., GAUR, T., LENGNER, C. J. & YOUNG, D. W. 2006. Networks and hubs for the transcriptional control of osteoblastogenesis. *Reviews in Endocrine & Metabolic Disorders,* 7**,** 1-16.

LIBERATI, A., ALTMAN, D. G., TETZLAFF, J., MULROW, C., GOTZSCHE, P. C., IOANNIDIS, J. P., CLARKE, M., DEVEREAUX, P. J., KLEIJNEN, J. & MOHER, D. 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ,* 339**,** b2700.

LIN, J., LU, H. & FENG, C. 1996. Ankylosing spondylitis and heterogeneity of HLA-B27 in Chinese. *Chinese Medical Journal (Engl.),* 109**,** 313-6.

LINK, T. M. 2012. Osteoporosis imaging: state of the art and advanced imaging. *Radiology,* 263**,** 3-17.

LLORENTE, I., MERINO, L., ORTIZ, A. M., ESCOLANO, E., GONZALEZ-ORTEGA, S., GARCIA-VICUNA, R., GARCIA-VADILLO, J. A., CASTANEDA, S. & GONZALEZ-ALVARO, I. 2017. Anti-citrullinated protein antibodies are associated with decreased bone mineral density: baseline data from a register of early arthritis patients. *Rheumatology International,* 37**,** 799-806.

LOPEZ-MEDINA, C., JIMENEZ-GOMEZ, Y., MOLTO, A., SCHIOTIS, R. E., MARZO-ORTEGA, H., VAN GAALEN, F. A., OZGOCMEN, S., DOUGADOS, M., CALVO-GUTIERREZ, J., CASTRO-VILLEGAS, M. C., COLLANTES-ESTEVEZ, E. & FONT-UGALDE, P. 2018. Cardiovascular risk factors in patients with spondyloarthritis from Northern European and Mediterranean countries: An ancillary study of the ASAS-COMOSPA project. *Joint, Bone, Spine: Revue du Rhumatisme,* 85**,** 447-453.

LORIES, R. J., DERESE, I., DE BARI, C. & LUYTEN, F. P. 2007. Evidence for uncoupling of inflammation and joint remodeling in a mouse model of spondylarthritis. *Arthritis and Rheumatism,* 56**,** 489-97.

LORIES, R. J. & HAROON, N. 2017. Evolving concepts of new bone formation in axial spondyloarthritis: Insights from animal models and human studies. *Best Practice & Research: Clinical Rheumatology,* 31**,** 877-886.

LORIES, R. J., LUYTEN, F. P. & DE VLAM, K. 2009. Progress in spondylarthritis. Mechanisms of new bone formation in spondyloarthritis. *Arthritis Research & Therapy,* 11**,** 221.

LOZA, E., JOVER, J. A., RODRIGUEZ, L. & CARMONA, L. 2009. Multimorbidity: prevalence, effect on quality of life and daily functioning, and variation of this effect when one condition is a rheumatic disease. *Seminars in Arthritis and Rheumatism,* 38**,** 312-9.

LUKAS, C., LANDEWE, R., SIEPER, J., DOUGADOS, M., DAVIS, J., BRAUN, J., VAN DER LINDEN, S. & VAN DER HEIJDE, D. 2009. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Annals of the Rheumatic Diseases,* 68**,** 18-24.

MA, T., MIYANISHI, K., SUEN, A., EPSTEIN, N. J., TOMITA, T., SMITH, R. L. & GOODMAN, S. B. 2004. Human interleukin-1-induced murine osteoclastogenesis is dependent on RANKL, but independent of TNF-alpha. *Cytokine,* 26**,** 138-44.

MAAS, F., ARENDS, S., VAN DER VEER, E., WINK, F., EFDE, M., BOOTSMA, H., BROUWER, E. & SPOORENBERG, A. 2016. Obesity Is Common in Axial Spondyloarthritis and Is Associated with Poor Clinical Outcome. *Journal of Rheumatology,* 43**,** 383-7.

MACHADO, P., LANDEWE, R., LIE, E., KVIEN, T. K., BRAUN, J., BAKER, D. & VAN DER HEIJDE, D. 2011. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Annals of the Rheumatic Diseases,* 70**,** 47-53.

MACHADO, P. M. & DEODHAR, A. 2019. Treat-to-target in axial spondyloarthritis: gold standard or fools' gold? *Current Opinion in Rheumatology,* 31**,** 344-348.

MACKEY, D. C., LUI, L. Y., CAWTHON, P. M., BAUER, D. C., NEVITT, M. C., CAULEY, J. A., HILLIER, T. A., LEWIS, C. E., BARRETT-CONNOR, E. & CUMMINGS, S. R. 2007. High-trauma fractures and low bone mineral density in older women and men. *JAMA,* 298**,** 2381-8.

MADER, R., VERLAAN, J. J., ESHED, I., JACOME, B. A., PUTTINI, P. S., ATZENI, F., BUSKILA, D., REINSHTEIN, E., NOVOFASTOVSKI, I., FAWAZ, A., KURT, V. & BARALIAKOS, X. 2017. Diffuse idiopathic skeletal hyperostosis (DISH): where we are now and where to go next. *RMD Open,* 3**,** e000472.

MAGREY, M. N. & KHAN, M. A. 2017. The Paradox of Bone Formation and Bone Loss in Ankylosing Spondylitis: Evolving New Concepts of Bone Formation and Future Trends in Management. *Current Rheumatology Reports,* 19**,** 17.

MAILLEFERT, J. F., AHO, L. S., EL MAGHRAOUI, A., DOUGADOS, M. & ROUX, C. 2001. Changes in bone density in patients with ankylosing spondylitis: a two-year follow-up study. *Osteoporosis International,* 12**,** 605-9.

MAKSYMOWYCH, W. P., CHIOWCHANWISAWAKIT, P., CLARE, T., PEDERSEN, S. J., OSTERGAARD, M. & LAMBERT, R. G. 2009. Inflammatory lesions of the spine on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis: evidence of a relationship between inflammation and new bone formation. *Arthritis and Rheumatism,* 60**,** 93-102.

MALOCHET-GUINAMAND, S., PEREIRA, B., TATAR, Z., TOURNADRE, A., MOLTO, A., DOUGADOS, M. & SOUBRIER, M. 2017. Prevalence and risk factors of low bone mineral density in spondyloarthritis and prevalence of vertebral fractures. *BMC Musculoskeletal Disorders,* 18**,** 357.

MANDL, P., NAVARRO-COMPAN, V., TERSLEV, L., AEGERTER, P., VAN DER HEIJDE, D., D'AGOSTINO, M. A., BARALIAKOS, X., PEDERSEN, S. J., JURIK, A. G., NAREDO, E., SCHUELLER-WEIDEKAMM, C., WEBER, U., WICK, M. C., BAKKER, P. A., FILIPPUCCI, E., CONAGHAN, P. G., RUDWALEIT, M., SCHETT, G., SIEPER, J., TARP, S., MARZO-ORTEGA, H., OSTERGAARD, M. & EUROPEAN LEAGUE AGAINST, R. 2015. EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. *Annals of the Rheumatic Diseases,* 74**,** 1327-39.

MANOLAGAS, S. C. 2010. From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis. *Endocrine Reviews,* 31**,** 266-300.

MAO, B., WU, W., DAVIDSON, G., MARHOLD, J., LI, M., MECHLER, B. M., DELIUS, H., HOPPE, D., STANNEK, P., WALTER, C., GLINKA, A. & NIEHRS, C. 2002. Kremen proteins are Dickkopf receptors that regulate Wnt/beta-catenin signalling. *Nature,* 417**,** 664-7.

MARHOFFER, W., STRACKE, H., MASOUD, I., SCHEJA, M., GRAEF, V., BOLTEN, W. & FEDERLIN, K. 1995. Evidence of impaired cartilage/bone turnover in patients with active ankylosing spondylitis. *Annals of the Rheumatic Diseases,* 54**,** 556-9.

MARTIN, T. M., ZHANG, G., LUO, J., JIN, L., DOYLE, T. M., RAJSKA, B. M., COFFMAN, J. E., SMITH, J. R., BECKER, M. D., MACKENSEN, F., KHAN, M. A.,

LEVINSON, R. D., SCHUMACHER, H. R., WADE, N. K., ROSENBAUM, J. T. & REVEILLE, J. D. 2005. A locus on chromosome 9p predisposes to a specific disease manifestation, acute anterior uveitis, in ankylosing spondylitis, a genetically complex, multisystem, inflammatory disease. *Arthritis and Rheumatism,* 52**,** 269-74.

MARZO-ORTEGA, H., MCGONAGLE, D., JARRETT, S., HAUGEBERG, G., HENSOR, E., O'CONNOR, P., TAN, A. L., CONAGHAN, P. G., GREENSTEIN, A. & EMERY, P. 2005. Infliximab in combination with methotrexate in active ankylosing spondylitis: a clinical and imaging study. *Annals of the Rheumatic Diseases,* 64**,** 1568-75.

MARZO-ORTEGA, H., SIEPER, J., KIVITZ, A., BLANCO, R., COHEN, M., MARTIN, R., READIE, A., RICHARDS, H. B. & PORTER, B. 2017. Secukinumab and Sustained Improvement in Signs and Symptoms of Patients With Active Ankylosing Spondylitis Through Two Years: Results From a Phase III Study. *Arthritis Care & Research,* 69**,** 1020-1029.

MASI, A. T. 1992. Do sex hormones play a role in ankylosing spondylitis? *Rheumatic Diseases Clinics of North America,* 18**,** 153-76.

MAU, W., ZEIDLER, H., MAU, R., MAJEWSKI, A., FREYSCHMIDT, J., STANGEL, W. & DEICHER, H. 1988. Clinical features and prognosis of patients with possible ankylosing spondylitis. Results of a 10-year followup. *Journal of Rheumatology,* 15**,** 1109-14.

MCDAID, O., HANLY, M. J., RICHARDSON, K., KEE, F., KENNY, R. A. & SAVVA, G. M. 2013. The effect of multiple chronic conditions on self-rated health, disability and quality of life among the older populations of Northern Ireland and the Republic of Ireland: a comparison of two nationally representative cross-sectional surveys. *BMJ Open,* 3.

MCGONAGLE, D., STOCKWIN, L., ISAACS, J. & EMERY, P. 2001. An enthesitis based model for the pathogenesis of spondyloarthropathy. additive effects of microbial adjuvant and biomechanical factors at disease sites. *Journal of Rheumatology,* 28**,** 2155-9.

MELTON, L. J., 3RD, THAMER, M., RAY, N. F., CHAN, J. K., CHESNUT, C. H., 3RD, EINHORN, T. A., JOHNSTON, C. C., RAISZ, L. G., SILVERMAN, S. L. & SIRIS, E. S. 1997. Fractures attributable to osteoporosis: report from the National Osteoporosis Foundation. *Journal of Bone and Mineral Research,* 12**,** 16-23.

MENOTTI, A., MULDER, I., NISSINEN, A., GIAMPAOLI, S., FESKENS, E. J. & KROMHOUT, D. 2001. Prevalence of morbidity and multimorbidity in elderly male populations and their impact on 10-year all-cause mortality: The FINE study (Finland, Italy, Netherlands, Elderly). *Journal of Clinical Epidemiology,* 54**,** 680-6.

MENSAH, K. A., MATHIAN, A., MA, L., XING, L., RITCHLIN, C. T. & SCHWARZ, E. M. 2010. Mediation of nonerosive arthritis in a mouse model of lupus by interferon-alpha-stimulated monocyte differentiation that is nonpermissive of osteoclastogenesis. *Arthritis and Rheumatism,* 62**,** 1127-37.

MERMERCI BASKAN, B., PEKIN DOGAN, Y., SIVAS, F., BODUR, H. & OZORAN, K. 2010. The relation between osteoporosis and vitamin D levels and disease activity in ankylosing spondylitis. *Rheumatology International,* 30**,** 375-81.

MESZAROS, S., TOTH, E., FERENCZ, V., CSUPOR, E., HOSSZU, E. & HORVATH, C. 2007. Calcaneous quantitative ultrasound measurements predicts vertebral fractures in idiopathic male osteoporosis. *Joint, Bone, Spine: Revue du Rhumatisme,* 74**,** 79-84.

MEUCCI, R. D., FASSA, A. G. & FARIA, N. M. 2015. Prevalence of chronic low back pain: systematic review. *Revista de Saúde Publica,* 49.

MIHAILOV, C., SURDU, O. & SURDU, T.-V. 2015. Evidence of Peloidotherapy Impact in Patients with Ankylosing Spondylitis. *JOURNAL OF ENVIRONMENTAL PROTECTION AND ECOLOGY,* 16**,** 751-757.

MIKYAS, Y., AGODOA, I. & YURGIN, N. 2014. A systematic review of osteoporosis medication adherence and osteoporosis-related fracture costs in men. *Appl Health Econ Health Policy,* 12**,** 267-77.

MILLER, P. D., HATTERSLEY, G., RIIS, B. J., WILLIAMS, G. C., LAU, E., RUSSO, L. A., ALEXANDERSEN, P., ZERBINI, C. A., HU, M. Y., HARRIS, A. G., FITZPATRICK, L. A., COSMAN, F. & CHRISTIANSEN, C. 2016. Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial. *JAMA,* 316**,** 722-33.

MILLER, P. D., NJEH, C. F., JANKOWSKI, L. G. & LENCHIK, L. 2002. What are the standards by which bone mass measurement at peripheral skeletal sites should be used in the diagnosis of osteoporosis? *Journal of Clinical Densitometry,* 5 Suppl**,** S39-45.

MITRA, D., ELVINS, D. M. & COLLINS, A. J. 1999a. Biochemical markers of bone metabolism in mild ankylosing spondylitis and their relationship with bone mineral density and vertebral fractures. *Journal of Rheumatology,* 26**,** 2201-4.

MITRA, D., ELVINS, D. M. & COLLINS, A. J. 1999b. Testosterone and testosterone free index in mild ankylosing spondylitis: relationship with bone mineral density and vertebral fractures. *Journal of Rheumatology,* 26**,** 2414-7.

MITRA, D., ELVINS, D. M., SPEDEN, D. J. & COLLINS, A. J. 2000. The prevalence of vertebral fractures in mild ankylosing spondylitis and their relationship to bone mineral density. *Rheumatology (Oxford, England),* 39**,** 85-9.

MOESTER, M. J., PAPAPOULOS, S. E., LOWIK, C. W. & VAN BEZOOIJEN, R. L. 2010. Sclerostin: current knowledge and future perspectives. *Calcified Tissue International,* 87**,** 99-107.

MOHAMAD, N.-V., SOELAIMAN, I.-N. & CHIN, K.-Y. 2016. A concise review of testosterone and bone health. *Clinical Interventions in Aging,* 11**,** 1317-1324.

MOKRAOUI, N. M., HAGGERTY, J., ALMIRALL, J. & FORTIN, M. 2016. Prevalence of self-reported multimorbidity in the general population and in primary care practices: a cross-sectional study. *BMC Research Notes,* 9**,** 314.

MOLL, J. M., HASLOCK, I., MACRAE, I. F. & WRIGHT, V. 1974. Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behcet's syndrome. *Medicine (Baltimore),* 53**,** 343-64.

MOLTO, A., ETCHETO, A., VAN DER HEIJDE, D., LANDEWE, R., VAN DEN BOSCH, F., BAUTISTA MOLANO, W., BURGOS-VARGAS, R., CHEUNG, P. P., COLLANTES-ESTEVEZ, E., DEODHAR, A., EL-ZORKANY, B., ERDES, S., GU, J.,

HAJJAJ-HASSOUNI, N., KILTZ, U., KIM, T. H., KISHIMOTO, M., LUO, S. F., MACHADO, P. M., MAKSYMOWYCH, W. P., MALDONADO-COCCO, J., MARZO-ORTEGA, H., MONTECUCCO, C. M., OZGOCMEN, S., VAN GAALEN, F. & DOUGADOS, M. 2016. Prevalence of comorbidities and evaluation of their screening in spondyloarthritis: results of the international cross-sectional ASAS-COMOSPA study. *Annals of the Rheumatic Diseases,* 75**,** 1016-23.

MONTALA, N., JUANOLA, X., COLLANTES, E., MUNOZ-GOMARIZ, E., GONZALEZ, C., GRATACOS, J., ZARCO, P., FERNANDEZ SUEIRO, J. L., MULERO, J., TORRE-ALONSO, J. C., BATLLE, E. & CARMONA, L. 2011. Prevalence of vertebral fractures by semiautomated morphometry in patients with ankylosing spondylitis. *Journal of Rheumatology,* 38**,** 893-7.

MORRIS, H. A., EASTELL, R., JORGENSEN, N. R., CAVALIER, E., VASIKARAN, S., CHUBB, S. A. P., KANIS, J. A., COOPER, C. & MAKRIS, K. 2017. Clinical usefulness of bone turnover marker concentrations in osteoporosis. *Clinica Chimica Acta,* 467**,** 34-41.

MUNTEAN, L., ROJAS-VARGAS, M., FONT, P., SIMON, S. P., REDNIC, S., SCHIOTIS, R., STEFAN, S., TAMAS, M. M., BOLOSIU, H. D. & COLLANTES-ESTEVEZ, E. 2011. Relative value of the lumbar spine and hip bone mineral density and bone turnover markers in men with ankylosing spondylitis. *Clinical Rheumatology,* 30**,** 691-5.

MUSTAFA, K. N., HAMMOUDEH, M. & KHAN, M. A. 2012. HLA-B27 Prevalence in Arab Populations and Among Patients with Ankylosing Spondylitis. *Journal of Rheumatology,* 39**,** 1675-7.

NAKAMURA, Y., SUZUKI, T. & KATO, H. 2017. Denosumab significantly improves bone mineral density with or without bisphosphonate pre-treatment in osteoporosis with rheumatoid arthritis : Denosumab improves bone mineral density in osteoporosis with rheumatoid arthritis. *Arch Osteoporos,* 12**,** 80.

NAKASHIMA, T., HAYASHI, M., FUKUNAGA, T., KURATA, K., OH-HORA, M., FENG, J. Q., BONEWALD, L. F., KODAMA, T., WUTZ, A., WAGNER, E. F., PENNINGER, J. M. & TAKAYANAGI, H. 2011. Evidence for osteocyte regulation of bone homeostasis through RANKL expression. *Nature Medicine,* 17**,** 1231-4.

NASSER, M., HAIDER, A., SAAD, F., KURTZ, W., DOROS, G., FIJAK, M., VIGNOZZI, L. & GOOREN, L. 2015. Testosterone therapy in men with Crohn's disease improves the clinical course of the disease: data from long-term observational registry study. *Hormone Molecular Biology and Clinical Investigation,* 22**,** 111-7.

NAVARRO-COMPAN, V., PLASENCIA-RODRIGUEZ, C., DE MIGUEL, E., BALSA, A., MARTIN-MOLA, E., SEOANE-MATO, D. & CANETE, J. D. 2016. Anti-TNF discontinuation and tapering strategies in patients with axial spondyloarthritis: a systematic literature review. *Rheumatology (Oxford, England),* 55**,** 1188-94.

NAVES, M., DIAZ-LOPEZ, J. B., GOMEZ, C., RODRIGUEZ-REBOLLAR, A., RODRIGUEZ-GARCIA, M. & CANNATA-ANDIA, J. B. 2003. The effect of vertebral fracture as a risk factor for osteoporotic fracture and mortality in a Spanish population. *Osteoporosis International,* 14**,** 520-4.

NAVICKAS, R., PETRIC, V. K., FEIGL, A. B. & SEYCHELL, M. 2016. Multimorbidity: What do we know? What should we do? *J Comorb,* 6**,** 4-11.

NEER, R. M., ARNAUD, C. D., ZANCHETTA, J. R., PRINCE, R., GAICH, G. A., REGINSTER, J. Y., HODSMAN, A. B., ERIKSEN, E. F., ISH-SHALOM, S., GENANT, H. K., WANG, O. & MITLAK, B. H. 2001. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *New England Journal of Medicine,* 344**,** 1434-41.

NIGIL HAROON, N., SZABO, E., RABOUD, J. M., MCDONALD-BLUMER, H., FUNG, L., JOSSE, R. G., INMAN, R. D. & CHEUNG, A. M. 2015. Alterations of bone mineral density, bone microarchitecture and strength in patients with ankylosing spondylitis: a cross-sectional study using high-resolution peripheral quantitative computerized tomography and finite element analysis. *Arthritis Research & Therapy,* 17**,** 377.

NIKIPHOROU, E., RAMIRO, S., VAN DER HEIJDE, D., NORTON, S., MOLTO, A., DOUGADOS, M., VAN DEN BOSCH, F., LANDEWE, R. & ASSESSMENT OF SPONDYLOARTHRITIS INTERNATIONAL SOCIETY COMORBIDITIES IN SPONDYLOARTHRITIS STUDY TASK, F. 2018. Association of Comorbidities in Spondyloarthritis With Poor Function, Work Disability, and Quality of Life: Results From the Assessment of SpondyloArthritis International Society Comorbidities in Spondyloarthritis Study. *Arthritis Care & Research,* 70**,** 1257-1262.

NJEH, C. F., BOIVIN, C. M. & LANGTON, C. M. 1997. The role of ultrasound in the assessment of osteoporosis: a review. *Osteoporosis International,* 7**,** 7-22.

O'DWYER, T., MONAGHAN, A., MORAN, J., O'SHEA, F. & WILSON, F. 2017. Behaviour change intervention increases physical activity, spinal mobility and quality of life in adults with ankylosing spondylitis: a randomised trial. *Journal of Physiotherapy,* 63**,** 30-39.

O'DWYER, T., O'SHEA, F. & WILSON, F. 2015. Decreased physical activity and cardiorespiratory fitness in adults with ankylosing spondylitis: a cross-sectional controlled study. *Rheumatology International,* 35**,** 1863-72.

O'DWYER, T., RAFFERTY, T., O'SHEA, F., GISSANE, C. & WILSON, F. 2014. Physical activity guidelines: is the message getting through to adults with rheumatic conditions? *Rheumatology (Oxford, England),* 53**,** 1812-7.

OBERMAYER-PIETSCH, B. M., LANGE, U., TAUBER, G., FRUHAUF, G., FAHRLEITNER, A., DOBNIG, H., HERMANN, J., AGLAS, F., TEICHMANN, J., NEECK, G. & LEB, G. 2003. Vitamin D receptor initiation codon polymorphism, bone density and inflammatory activity of patients with ankylosing spondylitis. *Osteoporosis International,* 14**,** 995-1000.

OKAMOTO, K., NAKASHIMA, T., SHINOHARA, M., NEGISHI-KOGA, T., KOMATSU, N., TERASHIMA, A., SAWA, S., NITTA, T. & TAKAYANAGI, H. 2017. Osteoimmunology: The Conceptual Framework Unifying the Immune and Skeletal Systems. *Physiological Reviews,* 97**,** 1295-1349.

OLIVIERI, I., D'ANGELO, S., PADULA, A., LECCESE, P. & PALAZZI, C. 2013. Spondyloarthritis with onset after age 45. *Current Rheumatology Reports,* 15**,** 374.

OMAIR, M. A., PAGNOUX, C., MCDONALD-BLUMER, H. & JOHNSON, S. R. 2013. Low bone density in systemic sclerosis. A systematic review. *Journal of Rheumatology,* 40**,** 1881-90.

ONG, T., KANTACHUVESIRI, P., SAHOTA, O. & GLADMAN, J. R. F. 2018. Characteristics and outcomes of hospitalised patients with vertebral fragility fractures: a systematic review. *Age and Ageing,* 47**,** 17-25.

ONGPHIPHADHANAKUL, B., RAJATANAVIN, R., CHAILURKIT, L., PIASEU, N., TEERARUNGSIKUL, K., SIRISRIRO, R., KOMINDR, S. & PUAVILAI, G. 1995. Serum testosterone and its relation to bone mineral density and body composition in normal males. *Clinical Endocrinology,* 43**,** 727-33.

OOSTVEEN, J., PREVO, R., DEN BOER, J. & VAN DE LAAR, M. 1999. Early detection of sacroiliitis on magnetic resonance imaging and subsequent development of sacroiliitis on plain radiography. A prospective, longitudinal study. *Journal of Rheumatology,* 26**,** 1953-8.

OZA, A., LU, N., SCHOENFELD, S. R., FISHER, M. C., DUBREUIL, M., RAI, S. K., ZHANG, Y. & CHOI, H. K. 2017. Survival benefit of statin use in ankylosing spondylitis: a general population-based cohort study. *Annals of the Rheumatic Diseases,* 76**,** 1737-1742.

OZDEMIR, O., GULSUN AKPINAR, M., INANICI, F. & HASCELIK, H. Z. 2012. Pulmonary abnormalities on high-resolution computed tomography in ankylosing spondylitis: relationship to disease duration and pulmonary function testing. *Rheumatology International,* 32**,** 2031-6.

PARFITT, A. M., MATHEWS, C. H., VILLANUEVA, A. R., KLEEREKOPER, M., FRAME, B. & RAO, D. S. 1983. Relationships between surface, volume, and thickness of iliac trabecular bone in aging and in osteoporosis. Implications for the microanatomic and cellular mechanisms of bone loss. *Journal of Clinical Investigation,* 72**,** 1396-409.

PARK, J. H., PARK, E. K., KOO, D. W., LEE, S., LEE, S. H., KIM, G. T. & LEE, S. G. 2017. Compliance and persistence with oral bisphosphonates for the treatment of osteoporosis in female patients with rheumatoid arthritis. *BMC Musculoskeletal Disorders,* 18**,** 152.

PARK, M. C., CHUNG, S. J., PARK, Y. B. & LEE, S. K. 2008. Bone and cartilage turnover markers, bone mineral density, and radiographic damage in men with ankylosing spondylitis. *Yonsei Medical Journal,* 49**,** 288-94.

PASCO, J. A., SEEMAN, E., HENRY, M. J., MERRIMAN, E. N., NICHOLSON, G. C. & KOTOWICZ, M. A. 2006. The population burden of fractures originates in women with osteopenia, not osteoporosis. *Osteoporosis International,* 17**,** 1404-9.

PATEL, R., BLAKE, G. M., RYMER, J. & FOGELMAN, I. 2000. Long-term precision of DXA scanning assessed over seven years in forty postmenopausal women. *Osteoporosis International,* 11**,** 68-75.

PEDERSEN, S. J., SORENSEN, I. J., LAMBERT, R. G., HERMANN, K. G., GARNERO, P., JOHANSEN, J. S., MADSEN, O. R., HANSEN, A., HANSEN, M. S., THAMSBORG, G., ANDERSEN, L. S., MAJGAARD, O., LOFT, A. G., ERLENDSSON, J., ASMUSSEN, K. H., JURIK, A. G., MOLLER, J., HASSELQUIST, M., MIKKELSEN, D. & OSTERGAARD, M. 2011. Radiographic progression is associated with resolution of systemic inflammation in patients with axial spondylarthritis treated with tumor necrosis factor alpha inhibitors: a study of radiographic progression, inflammation on magnetic resonance imaging, and circulating

biomarkers of inflammation, angiogenesis, and cartilage and bone turnover. *Arthritis and Rheumatism,* 63**,** 3789-800.

PEEL, N. F., JOHNSON, A., BARRINGTON, N. A., SMITH, T. W. & EASTELL, R. 1993. Impact of anomalous vertebral segmentation on measurements of bone mineral density. *Journal of Bone and Mineral Research,* 8**,** 719-23.

PEETERS, C. M., VISSER, E., VAN DE REE, C. L., GOSENS, T., DEN OUDSTEN, B. L. & DE VRIES, J. 2016. Quality of life after hip fracture in the elderly: A systematic literature review. *Injury,* 47**,** 1369-82.

PIKWER, M., GIWERCMAN, A., BERGSTROM, U., NILSSON, J. A., JACOBSSON, L. T. & TURESSON, C. 2014. Association between testosterone levels and risk of future rheumatoid arthritis in men: a population-based case-control study. *Annals of the Rheumatic Diseases,* 73**,** 573-9.

PINCUS, T., SUMMEY, J. A., SORACI, S. A., JR., WALLSTON, K. A. & HUMMON, N. P. 1983. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis and Rheumatism,* 26**,** 1346-53.

PODDUBNYY, D., BRANDT, H., VAHLDIEK, J., SPILLER, I., SONG, I. H., RUDWALEIT, M. & SIEPER, J. 2012. The frequency of non-radiographic axial spondyloarthritis in relation to symptom duration in patients referred because of chronic back pain: results from the Berlin early spondyloarthritis clinic. *Annals of the Rheumatic Diseases,* 71**,** 1998-2001.

PODDUBNYY, D. & SIEPER, J. 2014. Similarities and differences between nonradiographic and radiographic axial spondyloarthritis: a clinical, epidemiological and therapeutic assessment. *Current Opinion in Rheumatology,* 26**,** 377-83.

PODDUBNYY, D. & SIEPER, J. 2017. Mechanism of New Bone Formation in Axial Spondyloarthritis. *Current Rheumatology Reports,* 19**,** 55.

POTHUAUD, L., BARTHE, N., KRIEG, M. A., MEHSEN, N., CARCELLER, P. & HANS, D. 2009. Evaluation of the potential use of trabecular bone score to complement bone mineral density in the diagnosis of osteoporosis: a preliminary spine BMD-matched, case-control study. *Journal of Clinical Densitometry,* 12**,** 170-6.

PRATI, C., PUYRAVEAU, M., GUILLOT, X., VERHOEVEN, F. & WENDLING, D. 2017. Deaths Associated with Ankylosing Spondylitis in France from 1969 to 2009. *Journal of Rheumatology,* 44**,** 594-598.

PRAY, C., FEROZ, N. I. & NIGIL HAROON, N. 2017. Bone Mineral Density and Fracture Risk in Ankylosing Spondylitis: A Meta-Analysis. *Calcified Tissue International,* 101**,** 182-192.

QU, X., HUANG, X., JIN, F., WANG, H., HAO, Y., TANG, T. & DAI, K. 2013. Bone mineral density and all-cause, cardiovascular and stroke mortality: a meta-analysis of prospective cohort studies. *International Journal of Cardiology,* 166**,** 385-93.

RABIER, B., HERAUD, A., GRAND-LENOIR, C., WINZENRIETH, R. & HANS, D. 2010. A multicentre, retrospective case-control study assessing the role of trabecular bone score (TBS) in menopausal Caucasian women with low areal bone mineral density (BMDa): Analysing the odds of vertebral fracture. *Bone,* 46**,** 176-81.

RADFORD, E. P., DOLL, R. & SMITH, P. G. 1977. Mortality among patients with ankylosing spondylitis not given X-ray therapy. *New England Journal of Medicine,* 297**,** 572-6.

RADNER, H., YOSHIDA, K., FRITS, M., IANNACCONE, C., SHADICK, N. A., WEINBLATT, M., SMOLEN, J. S. & SOLOMON, D. H. 2015a. The impact of multimorbidity status on treatment response in rheumatoid arthritis patients initiating disease-modifying anti-rheumatic drugs. *Rheumatology (Oxford, England),* 54**,** 2076-84.

RADNER, H., YOSHIDA, K., HMAMOUCHI, I., DOUGADOS, M., SMOLEN, J. S. & SOLOMON, D. H. 2015b. Treatment Patterns of Multimorbid Patients with Rheumatoid Arthritis: Results from an International Cross-sectional Study. *Journal of Rheumatology,* 42**,** 1099-104.

RADNER, H., YOSHIDA, K., MJAAVATTEN, M. D., ALETAHA, D., FRITS, M., LU, B., IANNACCONE, C., SHADICK, N., WEINBLATT, M., HMAMOUCHI, I., DOUGADOS, M., SMOLEN, J. S. & SOLOMON, D. H. 2015c. Development of a multimorbidity index: Impact on quality of life using a rheumatoid arthritis cohort. *Seminars in Arthritis and Rheumatism,* 45**,** 167-73.

RADNER, H., YOSHIDA, K., SMOLEN, J. S. & SOLOMON, D. H. 2014. Multimorbidity and rheumatic conditions-enhancing the concept of comorbidity. *Nature Reviews: Rheumatology,* 10**,** 252-6.

RAJAMANOHARA, R., ROBINSON, J., RYMER, J., PATEL, R., FOGELMAN, I. & BLAKE, G. M. 2011. The effect of weight and weight change on the long-term precision of spine and hip DXA measurements. *Osteoporosis International,* 22**,** 1503-12.

RAMIREZ, J., NIETO-GONZALEZ, J. C., CURBELO RODRIGUEZ, R., CASTANEDA, S. & CARMONA, L. 2018. Prevalence and risk factors for osteoporosis and fractures in axial spondyloarthritis: A systematic review and meta-analysis. *Seminars in Arthritis and Rheumatism,* 48**,** 44-52.

RAMIRO, S., CLAUDEPIERRE, P., SEPRIANO, A., VAN LUNTEREN, M., MOLTO, A., FEYDY, A., ANTONIETTA D'AGOSTINO, M., LOEUILLE, D., DOUGADOS, M., REIJNIERSE, M. & VAN DER HEIJDE, D. 2018. Which scoring method depicts spinal radiographic damage in early axial spondyloarthritis best? Five-year results from the DESIR cohort. *Rheumatology (Oxford, England),* 57**,** 1991-2000.

RAMIRO, S., VAN DER HEIJDE, D., VAN TUBERGEN, A., STOLWIJK, C., DOUGADOS, M., VAN DEN BOSCH, F. & LANDEWE, R. 2014. Higher disease activity leads to more structural damage in the spine in ankylosing spondylitis: 12-year longitudinal data from the OASIS cohort. *Annals of the Rheumatic Diseases,* 73**,** 1455-61.

RANGANATHAN, V., GRACEY, E., BROWN, M. A., INMAN, R. D. & HAROON, N. 2017. Pathogenesis of ankylosing spondylitis - recent advances and future directions. *Nature Reviews: Rheumatology,* 13**,** 359-367.

RAUNER, M., STUPPHANN, D., HAAS, M., FERT, I., GLATIGNY, S., SIPOS, W., BREBAN, M. & PIETSCHMANN, P. 2009. The HLA-B27 transgenic rat, a model of spondyloarthritis, has decreased bone mineral density and increased RANKL to osteoprotegerin mRNA ratio. *Journal of Rheumatology,* 36**,** 120-6.

RAUNER, M., THIELE, S., FERT, I., ARAUJO, L. M., LAYH-SCHMITT, G., COLBERT, R. A., HOFBAUER, C., BERNHARDT, R., BURKI, A., SCHWIEDRZIK, J., ZYSSET, P. K., PIETSCHMANN, P., TAUROG, J. D., BREBAN, M. & HOFBAUER, L. C. 2015. Loss of bone strength in HLA-B27 transgenic rats is characterized by a high bone turnover and is mainly osteoclast-driven. *Bone,* 75**,** 183-91.

RECHEL, B., GRUNDY, E., ROBINE, J. M., CYLUS, J., MACKENBACH, J. P., KNAI, C. & MCKEE, M. 2013. Ageing in the European Union. *Lancet,* 381**,** 1312-22.

REDLICH, K. & SMOLEN, J. S. 2012. Inflammatory bone loss: pathogenesis and therapeutic intervention. *Nat Rev Drug Discov,* 11**,** 234-50.

REGINSTER, J.-Y., MINNE, H. W., SORENSEN, O. H., HOOPER, M., ROUX, C., BRANDI, M. L., LUND, B., ETHGEN, D., PACK, S., ROUMAGNAC, I., EASTELL, R. & GROUP, O. B. O. T. V. E. W. R. T. S. 2000. Randomized Trial of the Effects of Risedronate on Vertebral Fractures in Women with Established Postmenopausal Osteoporosis. *Osteoporosis International,* 11**,** 83-91.

REVEILLE, J. D. 2015. Biomarkers for diagnosis, monitoring of progression, and treatment responses in ankylosing spondylitis and axial spondyloarthritis. *Clinical Rheumatology,* 34**,** 1009-18.

REVEILLE, J. D., WITTER, J. P. & WEISMAN, M. H. 2012. Prevalence of axial spondylarthritis in the United States: estimates from a cross-sectional survey. *Arthritis Care & Research,* 64**,** 905-10.

RICHARD, N., HAROON, N., TOMLINSON, G., SARI, I., TOUMA, Z. & INMAN, R. 2018. Establishing the Minimal Clinically Important Difference (MCID) for the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) [abstract]. *Arthritis Rheumatol,* 70.

ROBINSON, P. C., CLAUSHUIS, T. A., CORTES, A., MARTIN, T. M., EVANS, D. M., LEO, P., MUKHOPADHYAY, P., BRADBURY, L. A., CREMIN, K., HARRIS, J., MAKSYMOWYCH, W. P., INMAN, R. D., RAHMAN, P., HAROON, N., GENSLER, L., POWELL, J. E., VAN DER HORST-BRUINSMA, I. E., HEWITT, A. W., CRAIG, J. E., LIM, L. L., WAKEFIELD, D., MCCLUSKEY, P., VOIGT, V., FLEMING, P., DEGLI-ESPOSTI, M., POINTON, J. J., WEISMAN, M. H., WORDSWORTH, B. P., REVEILLE, J. D., ROSENBAUM, J. T. & BROWN, M. A. 2015. Genetic dissection of acute anterior uveitis reveals similarities and differences in associations observed with ankylosing spondylitis. *Arthritis Rheumatol,* 67**,** 140-51.

ROBINSON, Y., SANDEN, B. & OLERUD, C. 2013. Increased occurrence of spinal fractures related to ankylosing spondylitis: a prospective 22-year cohort study in 17,764 patients from a national registry in Sweden. *Patient Safety in Surgery,* 7**,** 2.

ROSENBAUM, J. T. 2015. Uveitis in spondyloarthritis including psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel disease. *Clinical Rheumatology,* 34**,** 999-1002.

RUBIO VARGAS, R., VAN DEN BERG, R., VAN LUNTEREN, M., EZ-ZAITOUNI, Z., BAKKER, P. A., DAGFINRUD, H., RAMONDA, R., LANDEWE, R., MOLENAAR, E., VAN GAALEN, F. A. & VAN DER HEIJDE, D. 2016. Does body mass index (BMI) influence the Ankylosing Spondylitis Disease Activity Score in axial spondyloarthritis?: Data from the SPACE cohort. *RMD Open,* 2**,** e000283.

RUDWALEIT, M., HAIBEL, H., BARALIAKOS, X., LISTING, J., MARKER-HERMANN, E., ZEIDLER, H., BRAUN, J. & SIEPER, J. 2009a. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. *Arthritis and Rheumatism,* 60**,** 717-27.

RUDWALEIT, M., KHAN, M. A. & SIEPER, J. 2005. The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? *Arthritis and Rheumatism,* 52**,** 1000-8.

RUDWALEIT, M., LANDEWE, R., VAN DER HEIJDE, D., LISTING, J., BRANDT, J., BRAUN, J., BURGOS-VARGAS, R., COLLANTES-ESTEVEZ, E., DAVIS, J., DIJKMANS, B., DOUGADOS, M., EMERY, P., VAN DER HORST-BRUINSMA, I. E., INMAN, R., KHAN, M. A., LEIRISALO-REPO, M., VAN DER LINDEN, S., MAKSYMOWYCH, W. P., MIELANTS, H., OLIVIERI, I., STURROCK, R., DE VLAM, K. & SIEPER, J. 2009b. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Annals of the Rheumatic Diseases,* 68**,** 770-6.

RUDWALEIT, M., METTER, A., LISTING, J., SIEPER, J. & BRAUN, J. 2006. Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. *Arthritis and Rheumatism,* 54**,** 569-78.

RUDWALEIT, M., VAN DER HEIJDE, D., LANDEWE, R., AKKOC, N., BRANDT, J., CHOU, C. T., DOUGADOS, M., HUANG, F., GU, J., KIRAZLI, Y., VAN DEN BOSCH, F., OLIVIERI, I., ROUSSOU, E., SCARPATO, S., SORENSEN, I. J., VALLE-ONATE, R., WEBER, U., WEI, J. & SIEPER, J. 2011. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Annals of the Rheumatic Diseases,* 70**,** 25-31.

RUDWALEIT, M., VAN DER HEIJDE, D., LANDEWE, R., LISTING, J., AKKOC, N., BRANDT, J., BRAUN, J., CHOU, C. T., COLLANTES-ESTEVEZ, E., DOUGADOS, M., HUANG, F., GU, J., KHAN, M. A., KIRAZLI, Y., MAKSYMOWYCH, W. P., MIELANTS, H., SORENSEN, I. J., OZGOCMEN, S., ROUSSOU, E., VALLE-ONATE, R., WEBER, U., WEI, J. & SIEPER, J. 2009c. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Annals of the Rheumatic Diseases,* 68**,** 777-783.

RUEDA-GOTOR, J., GENRE, F., CORRALES, A., BLANCO, R., FUENTEVILLA, P., PORTILLA, V., EXPOSITO, R., MATA, C., PINA, T., GONZALEZ-JUANATEY, C., RODRIGUEZ-RODRIGUEZ, L. & GONZALEZ-GAY, M. A. 2018. Detection of high cardiovascular risk patients with ankylosing spondylitis based on the assessment of abdominal aortic calcium as compared to carotid ultrasound. *Arthritis Research & Therapy,* 20**,** 195.

RUSMAN, T., VAN VOLLENHOVEN, R. F. & VAN DER HORST-BRUINSMA, I. E. 2018. Gender Differences in Axial Spondyloarthritis: Women Are Not So Lucky. *Current Rheumatology Reports,* 20**,** 35.

SAAD, F., ROHRIG, G., VON HAEHLING, S. & TRAISH, A. 2017. Testosterone Deficiency and Testosterone Treatment in Older Men. *Gerontology,* 63**,** 144-156.

SAAG, K. G., PETERSEN, J., BRANDI, M. L., KARAPLIS, A. C., LORENTZON, M., THOMAS, T., MADDOX, J., FAN, M., MEISNER, P. D. & GRAUER, A. 2017. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. *New England Journal of Medicine,* 377**,** 1417-1427.

SANCHEZ-RIERA, L. & WILSON, N. 2017. Fragility Fractures & Their Impact on Older People. *Best Practice & Research: Clinical Rheumatology,* 31**,** 169-191.

SARIKAYA, S., BASARAN, A., TEKIN, Y., OZDOLAP, S. & ORTANCIL, O. 2007. Is osteoporosis generalized or localized to central skeleton in ankylosing spondylitis? *Journal of Clinical Rheumatology,* 13**,** 20-4.

SARKAR, M., BHARDWAJ, R., MADABHAVI, I. & KHATANA, J. 2015. Osteoporosis in chronic obstructive pulmonary disease. *Clinical medicine insights. Circulatory, respiratory and pulmonary medicine,* 9**,** 5-21.

SCHETT, G. 2011. Structural bone changes in spondyloarthritis: mechanisms, clinical impact and therapeutic considerations. *American Journal of the Medical Sciences,* 341**,** 269-71.

SCHETT, G., LORIES, R. J., D'AGOSTINO, M. A., ELEWAUT, D., KIRKHAM, B., SORIANO, E. R. & MCGONAGLE, D. 2017. Enthesitis: from pathophysiology to treatment. *Nature Reviews: Rheumatology,* 13**,** 731-741.

SCHOTTKER, B., JORDE, R., PEASEY, A., THORAND, B., JANSEN, E. H., GROOT, L., STREPPEL, M., GARDINER, J., ORDONEZ-MENA, J. M., PERNA, L., WILSGAARD, T., RATHMANN, W., FESKENS, E., KAMPMAN, E., SIGANOS, G., NJOLSTAD, I., MATHIESEN, E. B., KUBINOVA, R., PAJAK, A., TOPOR-MADRY, R., TAMOSIUNAS, A., HUGHES, M., KEE, F., BOBAK, M., TRICHOPOULOU, A., BOFFETTA, P. & BRENNER, H. 2014. Vitamin D and mortality: meta-analysis of individual participant data from a large consortium of cohort studies from Europe and the United States. *BMJ,* 348**,** g3656.

SCHOUSBOE, J. T. 2016. Epidemiology of Vertebral Fractures. *Journal of Clinical Densitometry,* 19**,** 8-22.

SCHOUSBOE, J. T., SHEPHERD, J. A., BILEZIKIAN, J. P. & BAIM, S. 2013. Executive summary of the 2013 International Society for Clinical Densitometry Position Development Conference on bone densitometry. *Journal of Clinical Densitometry,* 16**,** 455-66.

SCHUNEMANN, H. J., OXMAN, A. D., VIST, G. E., HIGGINS, J. P., DEEKS, J. J., GLASZIOU, P. & GUYATT, G. H. 2011. *Chapter 12: Interpreting results and drawing conclusions. In Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011),* The Cochrane Collaboration.

SCHWEITZER, A., HORN, J., MIKOLAJCZYK, R. T., KRAUSE, G. & OTT, J. J. 2015. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet,* 386**,** 1546-55.

SEELEY, D. G., BROWNER, W. S., NEVITT, M. C., GENANT, H. K., SCOTT, J. C. & CUMMINGS, S. R. 1991. Which fractures are associated with low appendicular bone mass in elderly women? The Study of Osteoporotic Fractures Research Group. *Annals of Internal Medicine,* 115**,** 837-42.

SEEMAN, E. 2002. Pathogenesis of bone fragility in women and men. *Lancet,* 359**,** 1841-50.

SEEMAN, E. & DELMAS, P. D. 2006. Bone quality--the material and structural basis of bone strength and fragility. *New England Journal of Medicine,* 354**,** 2250-61.

SENDUR, O. F., TURAN, Y., TASTABAN, E. & SERTER, M. 2009. Antioxidant status in patients with osteoporosis: a controlled study. *Joint, Bone, Spine: Revue du Rhumatisme,* 76**,** 514-8.

SHANE, E., BURR, D., ABRAHAMSEN, B., ADLER, R. A., BROWN, T. D., CHEUNG, A. M., COSMAN, F., CURTIS, J. R., DELL, R., DEMPSTER, D. W., EBELING, P. R., EINHORN, T. A., GENANT, H. K., GEUSENS, P., KLAUSHOFER, K., LANE, J. M., MCKIERNAN, F., MCKINNEY, R., NG, A., NIEVES, J., O'KEEFE, R., PAPAPOULOS, S., HOWE, T. S., VAN DER MEULEN, M. C., WEINSTEIN, R. S. & WHYTE, M. P. 2014. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *Journal of Bone and Mineral Research,* 29**,** 1-23.

SHEPHERD, J. A., SCHOUSBOE, J. T., BROY, S. B., ENGELKE, K. & LESLIE, W. D. 2015. Executive Summary of the 2015 ISCD Position Development Conference on Advanced Measures From DXA and QCT: Fracture Prediction Beyond BMD. *Journal of Clinical Densitometry,* 18**,** 274-86.

SHERLOCK, J. P., JOYCE-SHAIKH, B., TURNER, S. P., CHAO, C. C., SATHE, M., GREIN, J., GORMAN, D. M., BOWMAN, E. P., MCCLANAHAN, T. K., YEARLEY, J. H., EBERL, G., BUCKLEY, C. D., KASTELEIN, R. A., PIERCE, R. H., LAFACE, D. M. & CUA, D. J. 2012. IL-23 induces spondyloarthropathy by acting on ROR-gammat+ CD3+CD4-CD8- entheseal resident T cells. *Nature Medicine,* 18**,** 1069-76.

SHIN, J., SUNG, J., LEE, K. & SONG, Y. M. 2016. Genetic influence on the association between bone mineral density and testosterone in Korean men. *Osteoporosis International,* 27**,** 643-51.

SIEPER, J., DEODHAR, A., MARZO-ORTEGA, H., AELION, J. A., BLANCO, R., JUI-CHENG, T., ANDERSSON, M., PORTER, B. & RICHARDS, H. B. 2017. Secukinumab efficacy in anti-TNF-naive and anti-TNF-experienced subjects with active ankylosing spondylitis: results from the MEASURE 2 Study. *Annals of the Rheumatic Diseases,* 76**,** 571-592.

SIEPER, J., KLOPSCH, T., RICHTER, M., KAPELLE, A., RUDWALEIT, M., SCHWANK, S., REGOURD, E. & MAY, M. 2008. Comparison of two different dosages of celecoxib with diclofenac for the treatment of active ankylosing spondylitis: results of a 12-week randomised, double-blind, controlled study. *Annals of the Rheumatic Diseases,* 67**,** 323-9.

SIEPER, J., LENAERTS, J., WOLLENHAUPT, J., RUDWALEIT, M., MAZUROV, V. I., MYASOUTOVA, L., PARK, S., SONG, Y., YAO, R., CHITKARA, D. & VASTESAEGER, N. 2014. Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, Part 1. *Annals of the Rheumatic Diseases,* 73**,** 101-7.

SIEPER, J. & PODDUBNYY, D. 2017. Axial spondyloarthritis. *Lancet,* 390**,** 73-84.

SIEPER, J., RUDWALEIT, M., BARALIAKOS, X., BRANDT, J., BRAUN, J., BURGOS-VARGAS, R., DOUGADOS, M., HERMANN, K. G., LANDEWÉ, R., MAKSYMOWYCH, W. & VAN DER HEIJDE, D. 2009a. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Annals of the Rheumatic Diseases,* 68**,** ii1.

SIEPER, J., VAN DER HEIJDE, D., DOUGADOS, M., MEASE, P. J., MAKSYMOWYCH, W. P., BROWN, M. A., ARORA, V. & PANGAN, A. L. 2013. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Annals of the Rheumatic Diseases,* 72**,** 815-22.

SIEPER, J., VAN DER HEIJDE, D., LANDEWE, R., BRANDT, J., BURGOS-VAGAS, R., COLLANTES-ESTEVEZ, E., DIJKMANS, B., DOUGADOS, M., KHAN, M. A., LEIRISALO-REPO, M., VAN DER LINDEN, S., MAKSYMOWYCH, W. P., MIELANTS, H., OLIVIERI, I. & RUDWALEIT, M. 2009b. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). *Annals of the Rheumatic Diseases,* 68**,** 784-8.

SIMOES, D., ARAUJO, F. A., SEVERO, M., MONJARDINO, T., CRUZ, I., CARMONA, L. & LUCAS, R. 2017. Patterns and Consequences of Multimorbidity in the General Population: There is No Chronic Disease Management Without Rheumatic Disease Management. *Arthritis Care & Research,* 69**,** 12-20.

SIU, S., HARAOUI, B., BISSONNETTE, R., BESSETTE, L., ROUBILLE, C., RICHER, V., STARNINO, T., MCCOURT, C., MCFARLANE, A., FLEMING, P., KRAFT, J., LYNDE, C., GULLIVER, W., KEELING, S., DUTZ, J. & POPE, J. E. 2015. Meta-analysis of tumor necrosis factor inhibitors and glucocorticoids on bone density in rheumatoid arthritis and ankylosing spondylitis trials. *Arthritis Care & Research,* 67**,** 754-64.

SLOBODIN, G., REYHAN, I., AVSHOVICH, N., BALBIR-GURMAN, A., BOULMAN, N., ELIAS, M., FELD, J., MADER, R., MARKOVITZ, D., RIMAR, D., ROSNER, I., ROZENBAUM, M., ZISMAN, D. & ODEH, M. 2011. Recently diagnosed axial spondyloarthritis: gender differences and factors related to delay in diagnosis. *Clinical Rheumatology,* 30**,** 1075-80.

SMOLEN, J. S., BRAUN, J., DOUGADOS, M., EMERY, P., FITZGERALD, O., HELLIWELL, P., KAVANAUGH, A., KVIEN, T. K., LANDEWE, R., LUGER, T., MEASE, P., OLIVIERI, I., REVEILLE, J., RITCHLIN, C., RUDWALEIT, M., SCHOELS, M., SIEPER, J., WIT, M., BARALIAKOS, X., BETTERIDGE, N., BURGOS-VARGAS, R., COLLANTES-ESTEVEZ, E., DEODHAR, A., ELEWAUT, D., GOSSEC, L., JONGKEES, M., MACCARONE, M., REDLICH, K., VAN DEN BOSCH, F., WEI, J. C., WINTHROP, K. & VAN DER HEIJDE, D. 2014. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. *Annals of the Rheumatic Diseases,* 73**,** 6-16.

SONG, I. H., PODDUBNYY, D. A., RUDWALEIT, M. & SIEPER, J. 2008. Benefits and risks of ankylosing spondylitis treatment with nonsteroidal antiinflammatory drugs. *Arthritis and Rheumatism,* 58**,** 929-38.

SOROUSH, M., MIRTALEBI, M. & AHMADZADE, A. 2016. Comparison Evaluation of Bone Mineral Density in Patients with Ankylosing Spondylitis Before Treatment and

One Year After Treatment with Alendronate. *Biomedical and Pharmacology Journal,* 9**,** 537-542.

SPEDEN, D. J., CALIN, A. I., RING, F. J. & BHALLA, A. K. 2002. Bone mineral density, calcaneal ultrasound, and bone turnover markers in women with ankylosing spondylitis. *Journal of Rheumatology,* 29**,** 516-21.

SPENCER, D. G., STURROCK, R. D. & BUCHANAN, W. W. 1980. Ankylosing spondylitis: yesterday and today. *Medical History,* 24**,** 60-9.

STOLWIJK, C., BOONEN, A., VAN TUBERGEN, A. & REVEILLE, J. D. 2012. Epidemiology of spondyloarthritis. *Rheumatic Diseases Clinics of North America,* 38**,** 441-76.

STOLWIJK, C., ESSERS, I., VAN TUBERGEN, A., BOONEN, A., BAZELIER, M. T., DE BRUIN, M. L. & DE VRIES, F. 2015a. The epidemiology of extra-articular manifestations in ankylosing spondylitis: a population-based matched cohort study. *Annals of the Rheumatic Diseases,* 74**,** 1373-8.

STOLWIJK, C., VAN ONNA, M., BOONEN, A. & VAN TUBERGEN, A. 2016. Global Prevalence of Spondyloarthritis: A Systematic Review and Meta-Regression Analysis. *Arthritis Care & Research,* 68**,** 1320-31.

STOLWIJK, C., VAN TUBERGEN, A., CASTILLO-ORTIZ, J. D. & BOONEN, A. 2015b. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. *Annals of the Rheumatic Diseases,* 74**,** 65-73.

STONE, K. L., SEELEY, D. G., LUI, L. Y., CAULEY, J. A., ENSRUD, K., BROWNER, W. S., NEVITT, M. C. & CUMMINGS, S. R. 2003. BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. *Journal of Bone and Mineral Research,* 18**,** 1947-54.

STRAUB, R. H., CUTOLO, M. & PACIFICI, R. 2015. Evolutionary medicine and bone loss in chronic inflammatory diseases—A theory of inflammation-related osteopenia. *Seminars in Arthritis and Rheumatism,* 45**,** 220-228.

STRAUB, R. H., STRUHAROVA, S., SCHOLMERICH, J. & HARLE, P. 2002. No alterations of serum levels of adrenal and gonadal hormones in patients with ankylosing spondylitis. *Clinical and Experimental Rheumatology,* 20**,** S52-9.

STUCKI, G. & EWERT, T. 2005. How to assess the impact of arthritis on the individual patient: the WHO ICF. *Annals of the Rheumatic Diseases,* 64**,** 664-8.

SVEDBOM, A., BORGSTOM, F., HERNLUND, E., STROM, O., ALEKNA, V., BIANCHI, M. L., CLARK, P., CURIEL, M. D., DIMAI, H. P., JURISSON, M., KALLIKORM, R., LEMBER, M., LESNYAK, O., MCCLOSKEY, E., SANDERS, K. M., SILVERMAN, S., SOLODOVNIKOV, A., TAMULAITIENE, M., THOMAS, T., TOROPTSOVA, N., UUSKULA, A., TOSTESON, A. N. A., JONSSON, B. & KANIS, J. A. 2018. Quality of life for up to 18 months after low-energy hip, vertebral, and distal forearm fractures-results from the ICUROS. *Osteoporosis International,* 29**,** 557-566.

SVEDBOM, A., HERNLUND, E., IVERGARD, M., COMPSTON, J., COOPER, C., STENMARK, J., MCCLOSKEY, E. V., JONSSON, B. & KANIS, J. A. 2013. Osteoporosis in the European Union: a compendium of country-specific reports. *Arch Osteoporos,* 8**,** 137.

SZULC, P., MUNOZ, F., DUBOEUF, F., MARCHAND, F. & DELMAS, P. D. 2005. Bone mineral density predicts osteoporotic fractures in elderly men: the MINOS study. *Osteoporosis International,* 16**,** 1184-92.

SZULC, P., NAYLOR, K., HOYLE, N. R., EASTELL, R. & LEARY, E. T. 2017. Use of CTX-I and PINP as bone turnover markers: National Bone Health Alliance recommendations to standardize sample handling and patient preparation to reduce pre-analytical variability. *Osteoporosis International,* 28**,** 2541-2556.

TADA, M., INUI, K., SUGIOKA, Y., MAMOTO, K., OKANO, T., ANNO, S. & KOIKE, T. 2017. Use of bisphosphonate might be important to improve bone mineral density in patients with rheumatoid arthritis even under tight control: the TOMORROW study. *Rheumatology International,* 37**,** 999-1005.

TAKAYANAGI, H., KIM, S. & TANIGUCHI, T. 2002. Signaling crosstalk between RANKL and interferons in osteoclast differentiation. *Arthritis Research,* 4 Suppl 3**,** S227-32.

TAPIA-SERRANO, R., JIMENEZ-BALDERAS, F. J., MURRIETA, S., BRAVO-GATICA, C., GUERRA, R. & MINTZ, G. 1991. Testicular function in active ankylosing spondylitis. Therapeutic response to human chorionic gonadotrophin. *Journal of Rheumatology,* 18**,** 841-8.

TAUROG, J. D., CHHABRA, A. & COLBERT, R. A. 2016. Ankylosing Spondylitis and Axial Spondyloarthritis. *New England Journal of Medicine,* 374**,** 2563-74.

TAYLOR, H. G., BESWICK, E. J. & DAWES, P. T. 1991. Sulphasalazine in ankylosing spondylitis. A radiological, clinical and laboratory assessment. *Clinical Rheumatology,* 10**,** 43-8.

TEN DIJKE, P., KRAUSE, C., DE GORTER, D. J., LOWIK, C. W. & VAN BEZOOIJEN, R. L. 2008. Osteocyte-derived sclerostin inhibits bone formation: its role in bone morphogenetic protein and Wnt signaling. *Journal of Bone and Joint Surgery (American Volume),* 90 Suppl 1**,** 31-5.

TENGSTRAND, B., CARLSTROM, K. & HAFSTROM, I. 2009. Gonadal hormones in men with rheumatoid arthritis--from onset through 2 years. *Journal of Rheumatology,* 36**,** 887-92.

THOMSEN, K., JEPSEN, D. B., MATZEN, L., HERMANN, A. P., MASUD, T. & RYG, J. 2015. Is calcaneal quantitative ultrasound useful as a prescreen stratification tool for osteoporosis? *Osteoporosis International,* 26**,** 1459-75.

TIAN, A., MA, J., FENG, K., LIU, Z., CHEN, L., JIA, H. & MA, X. 2019. Reference markers of bone turnover for prediction of fracture: a meta-analysis. *Journal of Orthopaedic Surgery and Research,* 14**,** 68.

TOMS, T. E., PANOULAS, V. F., DOUGLAS, K. M., GRIFFITHS, H., SATTAR, N., SMITH, J. P., SYMMONS, D. P., NIGHTINGALE, P., METSIOS, G. S. & KITAS, G. D. 2010. Statin use in rheumatoid arthritis in relation to actual cardiovascular risk: evidence for substantial undertreatment of lipid-associated cardiovascular risk? *Annals of the Rheumatic Diseases,* 69**,** 683-8.

TOURNADRE, A., PEREIRA, B., GOSSEC, L., SOUBRIER, M. & DOUGADOS, M. 2018. Impact of comorbidities on fatigue in rheumatoid arthritis patients: results from a

nurse-led program for comorbidities management (COMEDRA). *Joint, Bone, Spine: Revue du Rhumatisme*.

TOUSSIROT, E., MICHEL, F. & WENDLING, D. 2001. Bone density, ultrasound measurements and body composition in early ankylosing spondylitis. *Rheumatology (Oxford, England),* 40**,** 882-8.

TOUSSIROT, E., RICARD-BLUM, S., DUMOULIN, G., CEDOZ, J. P. & WENDLING, D. 1999. Relationship between urinary pyridinium cross-links, disease activity and disease subsets of ankylosing spondylitis. *Rheumatology (Oxford, England),* 38**,** 21-7.

TOYRAS, J., KROGER, H. & JURVELIN, J. S. 1999. Bone properties as estimated by mineral density, ultrasound attenuation, and velocity. *Bone,* 25**,** 725-31.

TOYRAS, J., NIEMINEN, M. T., KROGER, H. & JURVELIN, J. S. 2002. Bone mineral density, ultrasound velocity, and broadband attenuation predict mechanical properties of trabecular bone differently. *Bone,* 31**,** 503-7.

TSOURDI, E., LANGDAHL, B., COHEN-SOLAL, M., AUBRY-ROZIER, B., ERIKSEN, E. F., GUANABENS, N., OBERMAYER-PIETSCH, B., RALSTON, S. H., EASTELL, R. & ZILLIKENS, M. C. 2017. Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS. *Bone,* 105**,** 11-17.

TURNER, M. J., SOWDERS, D. P., DELAY, M. L., MOHAPATRA, R., BAI, S., SMITH, J. A., BRANDEWIE, J. R., TAUROG, J. D. & COLBERT, R. A. 2005. HLA-B27 misfolding in transgenic rats is associated with activation of the unfolded protein response. *Journal of Immunology,* 175**,** 2438-48.

ULU, M. A., BATMAZ, I., DILEK, B. & CEVIK, R. 2014. Prevalence of osteoporosis and vertebral fractures and related factors in patients with ankylosing spondylitis. *Chinese Medical Journal (Engl.),* 127**,** 2740-7.

ULU, M. A., CEVIK, R. & DILEK, B. 2013. Comparison of PA spine, lateral spine, and femoral BMD measurements to determine bone loss in ankylosing spondylitis. *Rheumatology International,* 33**,** 1705-11.

UNDERWOOD, M. R. & DAWES, P. 1995. Inflammatory back pain in primary care. *British Journal of Rheumatology,* 34**,** 1074-7.

UPPAL, S. S., ABRAHAM, M., CHOWDHURY, R. I., KUMARI, R., PATHAN, E. M. & AL RASHED, A. 2006. Ankylosing spondylitis and undifferentiated spondyloarthritis in Kuwait: a comparison between Arabs and South Asians. *Clinical Rheumatology,* 25**,** 219-24.

VAN DEN AKKER, M., BUNTINX, F. & KNOTTNERUS, J. A. 1996. Comorbidity or multimorbidity. *European Journal of General Practice,* 2**,** 65-70.

VAN DEN BOSCH, F., KRUITHOF, E., BAETEN, D., DE KEYSER, F., MIELANTS, H. & VEYS, E. M. 2000. Effects of a loading dose regimen of three infusions of chimeric monoclonal antibody to tumour necrosis factor alpha (infliximab) in spondyloarthropathy: an open pilot study. *Annals of the Rheumatic Diseases,* 59**,** 428-33.

VAN DER HEIJDE, D., BARAF, H. S., RAMOS-REMUS, C., CALIN, A., WEAVER, A. L., SCHIFF, M., JAMES, M., MARKIND, J. E., REICIN, A. S., MELIAN, A. & DOUGADOS, M. 2005. Evaluation of the efficacy of etoricoxib in ankylosing

spondylitis: results of a fifty-two-week, randomized, controlled study. *Arthritis and Rheumatism,* 52**,** 1205-15.

VAN DER HEIJDE, D., BRAUN, J., DEODHAR, A., BARALIAKOS, X., LANDEWÉ, R., RICHARDS, H. B., PORTER, B. & READIE, A. 2018. Modified stoke ankylosing spondylitis spinal score as an outcome measure to assess the impact of treatment on structural progression in ankylosing spondylitis. *Rheumatology,* 58**,** 388-400.

VAN DER HEIJDE, D., BRAUN, J., DOUGADOS, M., SIEPER, J., PEDERSEN, R., SZUMSKI, A. & KOENIG, A. S. 2012. Sensitivity and discriminatory ability of the Ankylosing Spondylitis Disease Activity Score in patients treated with etanercept or sulphasalazine in the ASCEND trial. *Rheumatology (Oxford, England),* 51**,** 1894-905.

VAN DER HEIJDE, D., BREBAN, M., HALTER, D., DIVITTORIO, G., BRATT, J., CANTINI, F., KARY, S., PANGAN, A. L., KUPPER, H., RATHMANN, S. S., SIEPER, J. & MEASE, P. J. 2015. Maintenance of improvement in spinal mobility, physical function and quality of life in patients with ankylosing spondylitis after 5 years in a clinical trial of adalimumab. *Rheumatology (Oxford, England),* 54**,** 1210-9.

VAN DER HEIJDE, D., CALIN, A., DOUGADOS, M., KHAN, M. A., VAN DER LINDEN, S. & BELLAMY, N. 1999. Selection of instruments in the core set for DC-ART, SMARD, physical therapy, and clinical record keeping in ankylosing spondylitis. Progress report of the ASAS Working Group. Assessments in Ankylosing Spondylitis. *Journal of Rheumatology,* 26**,** 951-4.

VAN DER HEIJDE, D., LANDEWE, R., EINSTEIN, S., ORY, P., VOSSE, D., NI, L., LIN, S. L., TSUJI, W. & DAVIS, J. C., JR. 2008. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. *Arthritis and Rheumatism,* 58**,** 1324-31.

VAN DER HEIJDE, D., LIE, E., KVIEN, T. K., SIEPER, J., VAN DEN BOSCH, F., LISTING, J., BRAUN, J. & LANDEWE, R. 2009a. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. *Annals of the Rheumatic Diseases,* 68**,** 1811-8.

VAN DER HEIJDE, D., RAMIRO, S., LANDEWE, R., BARALIAKOS, X., VAN DEN BOSCH, F., SEPRIANO, A., REGEL, A., CIUREA, A., DAGFINRUD, H., DOUGADOS, M., VAN GAALEN, F., GEHER, P., VAN DER HORST-BRUINSMA, I., INMAN, R. D., JONGKEES, M., KILTZ, U., KVIEN, T. K., MACHADO, P. M., MARZO-ORTEGA, H., MOLTO, A., NAVARRO-COMPAN, V., OZGOCMEN, S., PIMENTEL-SANTOS, F. M., REVEILLE, J., RUDWALEIT, M., SIEPER, J., SAMPAIO-BARROS, P., WIEK, D. & BRAUN, J. 2017. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Annals of the Rheumatic Diseases,* 76**,** 978-991.

VAN DER HEIJDE, D., SALONEN, D., WEISSMAN, B. N., LANDEWE, R., MAKSYMOWYCH, W. P., KUPPER, H., BALLAL, S., GIBSON, E. & WONG, R. 2009b. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. *Arthritis Research & Therapy,* 11**,** R127.

VAN DER HEIJDE, D., SCHIFF, M. H., SIEPER, J., KIVITZ, A. J., WONG, R. L., KUPPER, H., DIJKMANS, B. A., MEASE, P. J. & DAVIS, J. C., JR. 2009c. Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for

up to 2 years: long-term results from the ATLAS trial. *Annals of the Rheumatic Diseases,* 68**,** 922-9.

VAN DER LINDEN, S., VALKENBURG, H. & CATS, A. 1983. The risk of developing ankylosing spondylitis in HLA-B27 positive individuals: a family and population study. *British Journal of Rheumatology,* 22**,** 18-9.

VAN DER LINDEN, S., VALKENBURG, H. A. & CATS, A. 1984. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis and Rheumatism,* 27**,** 361-8.

VAN DER WEIJDEN, M. A., CLAUSHUIS, T. A., NAZARI, T., LEMS, W. F., DIJKMANS, B. A. & VAN DER HORST-BRUINSMA, I. E. 2012. High prevalence of low bone mineral density in patients within 10 years of onset of ankylosing spondylitis: a systematic review. *Clinical Rheumatology,* 31**,** 1529-35.

VAN DER WEIJDEN, M. A. C., VAN DENDEREN, J. C., LEMS, W. F., HEYMANS, M. W., DIJKMANS, B. A. C. & VAN DER HORST-BRUINSMA, I. E. 2011. Low bone mineral density is related to male gender and decreased functional capacity in early spondylarthropathies. *Clinical Rheumatology,* 30**,** 497-503.

VAN DER ZEE-NEUEN, A., PUTRIK, P., RAMIRO, S., KESZEI, A., DE BIE, R., CHORUS, A. & BOONEN, A. 2016. Impact of Chronic Diseases and Multimorbidity on Health and Health Care Costs: The Additional Role of Musculoskeletal Disorders. *Arthritis Care & Research,* 68**,** 1823-1831.

VAN MECHELEN, M., GULINO, G. R., DE VLAM, K. & LORIES, R. 2018. Bone Disease in Axial Spondyloarthritis. *Calcified Tissue International,* 102**,** 547-558.

VAN PRAET, L., VAN DEN BOSCH, F. E., JACQUES, P., CARRON, P., JANS, L., COLMAN, R., GLORIEUS, E., PEETERS, H., MIELANTS, H., DE VOS, M., CUVELIER, C. & ELEWAUT, D. 2013. Microscopic gut inflammation in axial spondyloarthritis: a multiparametric predictive model. *Annals of the Rheumatic Diseases,* 72**,** 414-7.

VAN TUBERGEN, A. 2014. The changing clinical picture and epidemiology of spondyloarthritis. *Nature Reviews Rheumatology,* 11**,** 110.

VAN TUBERGEN, A., HEUFT-DORENBOSCH, L., SCHULPEN, G., LANDEWE, R., WIJERS, R., VAN DER HEIJDE, D., VAN ENGELSHOVEN, J. & VAN DER LINDEN, S. 2003. Radiographic assessment of sacroiliitis by radiologists and rheumatologists: does training improve quality? *Annals of the Rheumatic Diseases,* 62**,** 519-25.

VASIKARAN, S., EASTELL, R., BRUYÈRE, O., FOLDES, A. J., GARNERO, P., GRIESMACHER, A., MCCLUNG, M., MORRIS, H. A., SILVERMAN, S., TRENTI, T., WAHL, D. A., COOPER, C., KANIS, J. A. & GROUP, F. T. I.-I. B. M. S. W. 2011. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. *Osteoporosis International,* 22**,** 391-420.

VENCEVICIENE, L., BUTRIMIENE, I., VENCEVICIUS, R., SADAUSKIENE, E., KASIULEVICIUS, V. & SAPOKA, V. 2015. Factors associated with bone mineral density loss in patients with spondyloarthropathies: A 4-year follow-up study. *Medicina (Kaunas, Lithuania),* 51**,** 272-9.

VERONESE, N., CARRARO, S., BANO, G., TREVISAN, C., SOLMI, M., LUCHINI, C., MANZATO, E., CACCIALANZA, R., SERGI, G., NICETTO, D. & CEREDA, E. 2016. Hyperuricemia protects against low bone mineral density, osteoporosis and fractures: a systematic review and meta-analysis. *European Journal of Clinical Investigation,* 46**,** 920-930.

VIAPIANA, O., GATTI, D., IDOLAZZI, L., FRACASSI, E., ADAMI, S., TROPLINI, S., POVINO, M. R. & ROSSINI, M. 2014. Bisphosphonates vs infliximab in ankylosing spondylitis treatment. *Rheumatology (Oxford, England),* 53**,** 90-4.

VIOLAN, C., FOGUET-BOREU, Q., FLORES-MATEO, G., SALISBURY, C., BLOM, J., FREITAG, M., GLYNN, L., MUTH, C. & VALDERAS, J. M. 2014. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. *PloS One,* 9**,** e102149.

VON ELM, E., ALTMAN, D. G., EGGER, M., POCOCK, S. J., GOTZSCHE, P. C. & VANDENBROUCKE, J. P. 2007. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Annals of Internal Medicine,* 147**,** 573-7.

VON FRIESENDORFF, M., MCGUIGAN, F. E., WIZERT, A., ROGMARK, C., HOLMBERG, A. H., WOOLF, A. D. & AKESSON, K. 2016. Hip fracture, mortality risk, and cause of death over two decades. *Osteoporosis International,* 27**,** 2945-53.

VOSSE, D., LANDEWE, R., GARNERO, P., VAN DER HEIJDE, D., VAN DER LINDEN, S. & GEUSENS, P. 2008. Association of markers of bone- and cartilage-degradation with radiological changes at baseline and after 2 years follow-up in patients with ankylosing spondylitis. *Rheumatology (Oxford, England),* 47**,** 1219-22.

VOSSE, D., LANDEWÉ, R., VAN DER HEIJDE, D., VAN DER LINDEN, S., VAN STAA, T.-P. & GEUSENS, P. 2009. Ankylosing spondylitis and the risk of fracture: results from a large primary care-based nested case-control study. *Annals of the Rheumatic Diseases,* 68**,** 1839-1842.

WALSH, J. A., SONG, X., KIM, G. & PARK, Y. 2018. Evaluation of the comorbidity burden in patients with ankylosing spondylitis using a large US administrative claims data set. *Clinical Rheumatology,* 37**,** 1869-1878.

WANDERS, A., LANDEWE, R., DOUGADOS, M., MIELANTS, H., VAN DER LINDEN, S. & VAN DER HEIJDE, D. 2005. Association between radiographic damage of the spine and spinal mobility for individual patients with ankylosing spondylitis: can assessment of spinal mobility be a proxy for radiographic evaluation? *Annals of the Rheumatic Diseases,* 64**,** 988-94.

WANDERS, A. J., LANDEWE, R. B., SPOORENBERG, A., DOUGADOS, M., VAN DER LINDEN, S., MIELANTS, H., VAN DER TEMPEL, H. & VAN DER HEIJDE, D. M. 2004. What is the most appropriate radiologic scoring method for ankylosing spondylitis? A comparison of the available methods based on the Outcome Measures in Rheumatology Clinical Trials filter. *Arthritis and Rheumatism,* 50**,** 2622-32.

WANG, R. & WARD, M. M. 2018. Epidemiology of axial spondyloarthritis: an update. *Current Opinion in Rheumatology,* 30**,** 137-143.

WANG, S., HE, Q. & SHUAI, Z. 2018. Risk of serious infections in biological treatment of patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. *Clinical Rheumatology,* 37**,** 439-450.

WANG, X., YAN, S., LIU, C., XU, Y., WAN, L., WANG, Y., GAO, W., MENG, S., LIU, Y., LIU, R. & XU, D. 2016. Fracture risk and bone mineral density levels in patients with systemic lupus erythematosus: a systematic review and meta-analysis. *Osteoporosis International,* 27**,** 1413-1423.

WANG, Y. K., QIN, S. Q., MA, T., SONG, W., JIANG, R. Q., GUO, J. B., LI, K. & ZHANG, Y. M. 2017. Effects of teriparatide versus alendronate for treatment of postmenopausal osteoporosis: A meta-analysis of randomized controlled trials. *Medicine (Baltimore),* 96**,** e6970.

WEBER, U., ZUBLER, V., ZHAO, Z., LAMBERT, R. G., CHAN, S. M., PEDERSEN, S. J., OSTERGAARD, M., RUFIBACH, K. & MAKSYMOWYCH, W. P. 2015. Does spinal MRI add incremental diagnostic value to MRI of the sacroiliac joints alone in patients with non-radiographic axial spondyloarthritis? *Annals of the Rheumatic Diseases,* 74**,** 985-92.

WENDLING, D., PRATI, C., DEMATTEI, C., LOEUILLE, D., RICHETTE, P. & DOUGADOS, M. 2013. Anterior chest wall pain in recent inflammatory back pain suggestive of spondyloarthritis. data from the DESIR cohort. *Journal of Rheumatology,* 40**,** 1148-52.

WESTERVELD, L. A., VAN BEMMEL, J. C., DHERT, W. J., ONER, F. C. & VERLAAN, J. J. 2014. Clinical outcome after traumatic spinal fractures in patients with ankylosing spinal disorders compared with control patients. *Spine J,* 14**,** 729-40.

WESTERVELD, L. A., VERLAAN, J. J. & ONER, F. C. 2009. Spinal fractures in patients with ankylosing spinal disorders: a systematic review of the literature on treatment, neurological status and complications. *European Spine Journal,* 18**,** 145-56.

http://www.who.int/nmh/publications/ncd-status-report-2014/en/WHO. 2015. *Global status report on noncommunicable diseases 2014* [Online]. World Health Organization. Available: http://www.who.int/nmh/publications/ncd-status-report-2014/en/ [Accessed].

WILDBERGER, L., BOYADZHIEVA, V., HANS, D., STOILOV, N., RASHKOV, R. & AUBRY-ROZIER, B. 2016. Impact of lumbar syndesmophyte on bone health as assessed by bone density (BMD) and bone texture (TBS) in men with axial spondyloarthritis. *Joint, Bone, Spine: Revue du Rhumatisme*.

WINZENRIETH, R., DUFOUR, R., POTHUAUD, L. & HANS, D. 2010. A retrospective case-control study assessing the role of trabecular bone score in postmenopausal Caucasian women with osteopenia: analyzing the odds of vertebral fracture. *Calcified Tissue International,* 86**,** 104-9.

WORLD HEALTH ORGANIZATION 1998. *Guidelines for preclinical evaluation and clinical trials in osteoporosis*, World Health Organization.

WORLD HEALTH ORGANIZATION 2001. *International classification of functioning, disability and health: ICF*, Geneva: World Health Organization.

WORLD HEALTH ORGANIZATION 2013. Methodology and summary: Country profiles on nutrition, physical activity and obesity in the 53 WHO European Region Member States. *Copenhagen, Denmark: Author*.

WU, X., WEI, D., SUN, B. & WU, X. N. 2016. Poor medication adherence to bisphosphonates and high self-perception of aging in elderly female patients with osteoporosis. *Osteoporosis International,* 27**,** 3083-90.

WYSHAM, K. D., MURRAY, S. G., HILLS, N., YELIN, E. & GENSLER, L. S. 2017. Cervical Spinal Fracture and Other Diagnoses Associated With Mortality in Hospitalized Ankylosing Spondylitis Patients. *Arthritis Care & Research,* 69**,** 271-277.

XUE, A. L., WU, S. Y., JIANG, L., FENG, A. M., GUO, H. F. & ZHAO, P. 2017. Bone fracture risk in patients with rheumatoid arthritis: A meta-analysis. *Medicine (Baltimore),* 96**,** e6983.

YAMADA, A., IWATA, T., YAMATO, M., OKANO, T. & IZUMI, Y. 2013. Diverse functions of secreted frizzled-related proteins in the osteoblastogenesis of human multipotent mesenchymal stromal cells. *Biomaterials,* 34**,** 3270-8.

YANG, S., FESKANICH, D., WILLETT, W. C., ELIASSEN, A. H. & WU, T. 2014. Association between global biomarkers of oxidative stress and hip fracture in postmenopausal women: a prospective study. *Journal of Bone and Mineral Research,* 29**,** 2577-83.

YAZICI, H. 2009. Diagnostic versus classification criteria - a continuum. *Bulletin of the NYU Hospital for Joint Diseases,* 67**,** 206-8.
YILMAZ, N. & OZASLAN, J. 2000. Biochemical bone turnover markers in patients with ankylosing spondylitis. *Clinical Rheumatology,* 19**,** 92-8.

YU, W., GLUER, C. C., GRAMPP, S., JERGAS, M., FUERST, T., WU, C. Y., LU, Y., FAN, B. & GENANT, H. K. 1995. Spinal bone mineral assessment in postmenopausal women: a comparison between dual X-ray absorptiometry and quantitative computed tomography. *Osteoporosis International,* 5**,** 433-9.

ZAGAR, I., DELIMAR, V., COTA, S., PERIC, D., LAKTASIC-ZERJAVIC, N. & PERIC, P. 2019. Correspondence of vitamin D status with functional scores and disease activity among Croatian patients with ankylosing spondylitis: a preliminary study. *Psychiatr Danub,* 31**,** 105-111.

ZEBAZE, R. M., GHASEM-ZADEH, A., BOHTE, A., IULIANO-BURNS, S., MIRAMS, M., PRICE, R. I., MACKIE, E. J. & SEEMAN, E. 2010. Intracortical remodelling and porosity in the distal radius and post-mortem femurs of women: a cross-sectional study. *Lancet,* 375**,** 1729-36.

ZEBOULON, N., DOUGADOS, M. & GOSSEC, L. 2008. Prevalence and characteristics of uveitis in the spondyloarthropathies: a systematic literature review. *Annals of the Rheumatic Diseases,* 67**,** 955-9.

ZERBINI, C. A. F., CLARK, P., MENDEZ-SANCHEZ, L., PEREIRA, R. M. R., MESSINA, O. D., UNA, C. R., ADACHI, J. D., LEMS, W. F., COOPER, C. & LANE, N. E. 2017. Biologic therapies and bone loss in rheumatoid arthritis. *Osteoporosis International,* 28**,** 429-446.

ZHA, X. Y., HU, Y., PANG, X. N., CHANG, G. L. & LI, L. 2015. Diagnostic value of osteoporosis self-assessment tool for Asians (OSTA) and quantitative bone ultrasound (QUS) in detecting high-risk populations for osteoporosis among elderly Chinese men. *Journal of Bone and Mineral Metabolism,* 33**,** 230-8.

ZHANG, P., LI, Q., WEI, Q., LIAO, Z., LIN, Z., FANG, L. & GU, J. 2015. Serum Vitamin D and Pyridinoline Cross-Linked Carboxyterminal Telopeptide of Type I Collagen in Patients with Ankylosing Spondylitis. *Biomed Res Int,* 2015**,** 543806.

ZHAO, S., DUFFIELD, S. J., MOOTS, R. J. & GOODSON, N. J. 2014. Systematic review of association between vitamin D levels and susceptibility and disease activity of ankylosing spondylitis. *Rheumatology (Oxford, England),* 53**,** 1595-603.

ZHAO, S., THONG, D., MILLER, N., DUFFIELD, S. J., HUGHES, D. M., CHADWICK, L. & GOODSON, N. J. 2018. The prevalence of depression in axial spondyloarthritis and its association with disease activity: a systematic review and meta-analysis. *Arthritis Research & Therapy,* 20**,** 140.

ZHAO, S. S., RADNER, H., SIEBERT, S., DUFFIELD, S. J., THONG, D., HUGHES, D. M., MOOTS, R. J., SOLOMON, D. H. & GOODSON, N. J. 2019. Comorbidity burden in axial spondyloarthritis: a cluster analysis. *Rheumatology (Oxford, England)*.

ZHAO, S. Z., THONG, D., DUFFIELD, S. & GOODSON, N. 2017. Vitamin D Deficiency in Axial Spondyloarthritis is Associated With Higher Disease Activity. *Arch Rheumatol,* 32**,** 209-215.

ZMUDA, J. M., CAULEY, J. A., GLYNN, N. W. & FINKELSTEIN, J. S. 2000. Posterior-anterior and lateral dual-energy x-ray absorptiometry for the assessment of vertebral osteoporosis and bone loss among older men. *Journal of Bone and Mineral Research,* 15**,** 1417-24.

ZOCHLING, J. 2011. Measures of symptoms and disease status in ankylosing spondylitis: Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), and Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S). *Arthritis Care & Research,* 63 Suppl 11**,** S47-58.

Appendix A Published manuscripts from this thesis

Published manuscripts

A.1 Fitzgerald G, Gallagher P, O' Shea FD. (2020) Multimorbidity is common in axial spondyloarthropathy and is associated with worse disease outcomes: results from the Ankylosing Spondylitis Registry of Ireland cohort. *Journal of Rheumatology*. Feb;47(2):218-226. Epub 2019 May 15.

A.2 Fitzgerald GE, Anachebe T, McCarroll KG, O'Shea FD. (2020) Calcaneal quantitative ultrasound has a role in out ruling low bone mineral density in axial spondyloarthropathy. *Clinical Rheumatology*. Jan 17. doi: 10.1007/s10067-019-04876-9. [Epub ahead of print].

A.3 Fitzgerald G, Anachebe T, McCarroll K, O' Shea F. (2020) Measuring bone density in axial SpA: time to turn things on their side? *International Journal of Rheumatic Diseases*. Jan 7. doi: 10.1111/1756-185X.13765. [Epub ahead of print].

A.4 Fitzgerald G, O' Shea F. (2017) The fascinating paradox of osteoporosis in axial spondyloarthropathy. *Journal of Rheumatology.* 44(12):1767-76.

Published conference abstracts

A.5 Fitzgerald G, Wyse J, Anachebe T, Mullan R, Kane D, McCarroll K, O' Shea F. (2018) Lateral DXA More Effective in Detecting Osteoporosis Than Conventional DXA in Axial Spondyloarthropathy [abstract]. *Arthritis and Rheumatology*; 70 (suppl 10). https://acrabstracts.org/abstract/lateral-dxa-more-effective-in-detecting-osteoporosis-than-conventional-dxa-in-axial-spondyloarthropathy/. Accessed November 27, 2018.

A.6 Fitzgerald G, Anachebe T, Mullan R, Kane D, McCarroll K, O' Shea F. (2018) Quantitative Ultrasound of the Calcaneus Has a Role to Play in Detecting Low Bone Mineral Density in Axial Spondyloarthropathy Patients [abstract]. *Arthritis and Rheumatology*.; 70 (suppl 10). https://acrabstracts.org/abstract/quantitative-ultrasound-of-the-calcaneus-has-a-role-to-play-in-detecting-low-bone-mineral-density-in-axial-spondyloarthropathy-patients/. Accessed November 27, 2018.

A.7 Fitzgerald G, Anachebe T, Mullan R, Kane D, McCarroll K, O' Shea F. (2018) Higher Serum Uric Acid Levels Protect Against Osteoporosis in Patients with Axial Spondyloarthropathy [abstract]. *Arthritis and Rheumatology*. 2018; 70 (suppl 10). https://acrabstracts.org/abstract/higher-serum-uric-acid-levels-protect-against-osteoporosis-in-patients-with-axial-spondyloarthropathy/. Accessed November 27, 2018.

A.8 Fitzgerald GE, Anachebe T, McCarroll K, O' Shea F. (2018) Syndesmophytes prevent accurate DXA assessment of the spine in axial spondyloarthropathy [abstract]; *Clinical and Experimental Rheumatology*;36:742.

A.9 Fitzgerald GE, Anachebe T, McCarroll K, O' Shea F. (2018) Osteoporosis commonly occurs in axial spondyloarthropathy [abstract]. *Clinical and Experimental Rheumatology*;36:742.

A.10 Fitzgerald G, Anachebe T, O' Shea F. (2018) FRI0196 Traditional dxa underestimates bone mineral density of the spine in axial spondyloarthropathy [abstract]. *Annals of the Rheumatic Diseases*;77:639. http://dx.doi.org/10.1136/annrheumdis-2018-eular.6296

A.11 Fitzgerald G, Anachebe T, Mullan R, Kane D, McCarroll K, O' Shea F. (2018) Quantitative Ultrasound of the Calcaneus Has a Role to Play in Detecting Low Bone Mineral Density in Axial Spondyloarthropathy Patients [abstract]. *Arthritis and Rheumatol*ogy; 70 (suppl 10). https://acrabstracts.org/abstract/quantitative-ultrasound-of-the-calcaneus-has-a-role-to-play-in-detecting-low-bone-mineral-density-in-axial-spondyloarthropathy-patients/. Accessed November 27, 2018.

A.12 Fitzgerald G, Anachebe T, O' Shea F. (2018) THU0255 Low bone mineral density is common in axial spondyloarthropathy [abstract]. *Annals of the Rheumatic Diseases*;77:347. http://dx.doi.org/10.1136/annrheumdis-2018-eular.6287.

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Multimorbidity is Common in Axial Spondyloarthropathy and is Associated with Worse Disease Outcomes: Results from the ASRI cohort

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DOI: 10.3899/jrheum.181415
http://www.jrheum.org/content/early/2019/05/13/jrheum.181415

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Multimorbidity is Common in Axial Spondyloarthropathy and is Associated with Worse Disease Outcomes: Results from the ASRI cohort

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Key Indexing Terms:

Spondyloarthropathies; Axial Spondyloarthopathy; Multiple chronic conditions; Outcome measures.

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Funding

ASRI is supported by an unrestricted grant from Pfizer Pharmaceuticals and AbbVie Pharmaceuticals. GF is a recipient of the Bresnihan-Molloy Scholarship from the Royal College of Physicians of Ireland, funded by AbbVie pharmaceuticals. The funders had no role in the design of the study, collection of the data, analysis and interpretation of the data or any part of manuscript preparation.

Conflict of interest: The authors declare no conflicts of interest.

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ABSTRACT

Objective

Multimorbidity, the co-existence of 2 or more conditions in an individual, is associated with morbidity and mortality in the general population. This study aims to describe the prevalence of multimorbidity in axial spondyloarthropathy (axSpA) and assess its association with disease outcome measures.

Methods

This cross-sectional study was conducted within the Ankylosing Spondylitis Registry of Ireland (ASRI) cohort. Structured standardised assessment was performed. Multimorbidity was considered as the presence of at least 1 physician-diagnosed chronic condition (excluding extra-articular manifestations) in addition to axSpA. Validated outcome measures were collected: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), Health Assessment Questionnaire (HAQ), AS Quality of Life (ASQoL), Bath AS Metrology Index (BASMI). Adjusted multiple regression was performed to investigate the association between multimorbidity and disease outcomes.

Results

A total of 734 patients from 12 centres were included: 77% male, mean (SD) age 45 (12) years. Of the cohort, 55% (n=403) are multimorbid. Multimorbid patients are significantly ($p<0.01$) older than axSpA-only patients (50 (12) v 40 (11) years). Obesity is the most prevalent chronic condition, affecting 27%. Multimorbid patients have more severe disease than patients with axSpA only. After adjusting for confounders, multimorbidity was associated with higher BASDAI (ß=0.7, 95% CI 0.34 to 1.05), BASMI (ß=0.45, 95% CI 0.09 to 0.80), BASFI (ß=0. 5, 95% CI 0.23 to 0.78), HAQ (ß=0.07, 95% CI 0.00 to 0.13) and ASQoL (ß=0.87, 95% CI 0.28 to 1.46).

Conclusion

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Multimorbidity is prevalent in axSpA and is associated with more severe disease.

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INTRODUCTION

The dramatic increase in life expectancy of modern times is an important accomplishment (1, 2). Population growth has been accompanied by many challenges (3, 4), including projected increases in age-related expenditure and associated economic burden. A simple aspiration to live longer is no longer the goal. A delayed onset of morbidity and functional decline, termed "compression of morbidity" (5), is now the ambition, where people live longer but with less chronic disease. Unfortunately, it appears that old age is instead accompanied by a greater disease burden (6), namely noncommunicable diseases, now the biggest threat to mortality worldwide (7).

In order to cope with ageing populations, health systems must adapt (3). Current clinical practise guidelines focus on individual co-morbidities, without giving adequate guidance on managing patients with multiple chronic conditions (8). However, with pressure to delay the onset of functional decline and facilitate people to remain effective members of society for longer, swapping the concept of co-morbidity for multimorbidity is needed (8). Multimorbidity shifts our focus from a narrow view of considering each condition in isolation to a more holistic approach, whereby the patient is considered as the centre of care and all aspects of their condition are considered together (8, 9).

Although the definition can vary, multimorbidity is widely accepted as the presence of 2 or more chronic conditions in the one individual, without specifying the index disease (10). Multimorbidity estimates range from 13-95%, with prevalence increasing with age (11, 12). Multimorbid patients have increased mortality, more disability, worse quality of life and greater utilisation of healthcare resources (13-15); in some cases, 25% of the population accounts for more than 50% of health utilisation (15). Musculoskeletal disease (MSD) is common in multimorbidity patterns (16) and serves to intensify the impact (17, 18).

In rheumatoid arthritis (RA), 62-65% of patients are multimorbid (19, 20). Multimorbid RA patients have worse physical function (9) and lower rates of disease control (21).

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A growing body of work has examined the burden of co-morbidities in axSpA (22-26). Mortality is known to be increased in axSpA patients compared to age- and sex-matched controls (25-27). The recent Assessment of SpondyloArthritis Society (ASAS) – COMOSPA study (23) has outlined the comorbidity profile of axSpA patients, particularly highlighting the frequency of osteoporosis and peptic ulcer disease. Cardiovascular-related co-morbidity is also more prevalent in AS (28, 29). Co-morbidity adds to the burden of disease in SpA patients, adversely influencing physical function and quality of life (24). ASAS/European League Against Rheumatism (EULAR) recommendations for management of axSpA suggest that treatment should be tailored to take comorbidities into consideration (30), but no specific guidelines are available. However, little is known about the burden of multimorbidity in axSpA, despite recognition that better knowledge of multimorbidity is crucial to allow sustainable models of care to be established (8). In modern society, increasing emphasis is being placed on compression of morbidity, therefore it is important to understand the impact of multimorbidity in axSpA patients. To our knowledge, there is no literature looking at the prevalence of multimorbidity and associated relationships in patients with axSpA.

Therefore, the aims of this study are to determine:

1. prevalence of multimorbidity within a well-characterised real-life axSpA cohort
2. relationships between multimorbidity and disease outcomes.

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MATERIALS AND METHODS

ASRI study design & patient recruitment

This study was conducted within the framework of the Ankylosing Spondylitis Registry of Ireland (ASRI) cohort. ASRI is a large observational cross-sectional multicentre cohort study, which is ongoing. It was established in 2013, with the primary objective to measure the burden of axSpA disease in the Irish population and identify predictors of poor disease outcome.

Consecutive patients are invited to partake in ASRI if they have a clinical diagnosis of axSpA, made by a Rheumatologist, and have attended secondary or tertiary care in the preceding 3 years. Patients are excluded if they have cognitive or other impairment which prohibits informed consent. Each centre has a designated sub-investigator with responsibility for local oversight. Accuracy of the data collected is monitored quarterly by PG. The primary investigator (FOS) has responsibility for overall oversight of the database. To date, 12 centres in Ireland have recruited patients and contributed data to ASRI.

Written informed consent is obtained from all patients. Ethical approval was originally obtained from the Tallaght University Hospital/St. James's Hospital Joint Research Ethics Committee (REC reference: 2013/21/06) and was subsequently approved in each participating centre.

Data collection

A trained study investigator collected data according to a standard protocol in a structured face-to-face visit. The medical record was reviewed as required to obtain information not available directly from the patient. The following data was entered into an electronic centralised report form:

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- Demographics: age, sex, ethnicity, marital status, employment status, alcohol intake, smoking status (current/past/never), family history of SpA (AS, AxSpA, psoriasis or psoriatic arthritis).
- Disease characteristics: age of symptom onset, duration of disease, delay to diagnosis, history of extra-articular manifestations (EAM) (uveitis, psoriasis, inflammatory bowel disease), other SpA features (enthesitis, dactylitis, peripheral arthritis), current and previous treatment (non-steroidal anti-inflammatories (NSAIDs), methotrexate, sulfasalazine, biologics), human leukocyte antigen (HLA)-B27 status, highest recorded erythrocyte sedimentation rate (ESR), current ESR (measured on the day), highest recorded C-reactive protein (CRP), current CRP (measured on the day).
- Morbidities: considered present if patient had history of physician diagnosis of any of the following conditions known to be prevalent in SpA (23): ischaemic heart disease, cerebrovascular disease, hypertension, hyperlipidaemia, diabetes mellitus, peptic ulcer disease, tuberculosis, osteoporosis, depression, cancer (melanoma, non-melanoma skin cancer, lung, breast, gastrointestinal, genitourinary, lymphoma, haematological, other). Additionally obesity (recorded as a body mass index (BMI) of greater than 30 mg/kg^2, as per the WHO criteria, based on the weight and height measurements taken by the investigator during the assessment) and alcohol excess (considered as an alcohol consumption of greater than 21 units in men and 14 units in women, as per national guidelines (31), and was based on the patient's self-report of alcohol consumption) were collected. Patient medical records were used as required to confirm the presence or absence of each of these co-morbidities. EAMs were not considered as additional morbidities.
- Physical examination: tragus-to-wall, cervical rotation, chest expansion, modified Schober test, lumbar side flexion, intermalleolar distance – all performed according to standardised technique (32); current blood pressure, height (measured in centimetres), weight (measured in kilograms), waist circumference (measured in cm).

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- Dual-energy x-ray absorptiometry (DXA): most recent DXA result was obtained (if performed) and osteoporosis defined according to the World Health Organisation (WHO) (33).

Outcome measures

The following validated patient-reported outcomes were collected:

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI): measured on a scale of 0-10; higher scores indicate more severe disease (34).
- Bath AS Functional Index (BASFI): measured on a scale of 0-10; higher scores indicate worse function (35).
- Health Assessment Questionnaire (HAQ): assessed on a scale of 0-3; 0 indicates no disability and 3 indicates large burden of disability (36).
- AS Quality of Life (ASQoL): assessed on a scale of 0-18; higher scores indicate worse QoL (37).

Bath AS Metrology Index (BASMI) assessed spinal mobility on a scale of 0-10; higher scores indicate worse spinal mobility (32).

Multimorbidity

Morbidity is defined as the presence of a chronic condition in a patient. We defined multimorbidity as the presence of at least two chronic conditions in one person (10, 38). Severity of multimorbidity was assessed by counting the number of chronic conditions in addition to axSpA present in an individual (20, 39). Of note, EAMs were not considered a separate morbidity.

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Statistical analysis

Descriptive statistics are presented as mean with standard deviation (SD), median with 25th and 75th percentiles or frequencies with percentage as appropriate. Independent 2-tailed T-tests, Mann-Whitney U test or Analysis of Variance (ANOVA) were performed on continuous data as indicated to explore differences between groups. Chi-square tests compared categorical variables. Tukey's honestly significant difference (HSD) test controlled for multiple comparisons.

We developed separate models determining the association between (1) being multimorbid and (2) worsening multimorbidity, defined by number of additional chronic conditions, and disease outcome measures. BASDAI, BASMI, BASFI, ASQoL and HAQ were individually treated as dependent variables. Initially we explored univariable demographic, treatment and disease-related characteristics associated with each outcome. To control for the effects of these characteristics, we built a model using all variables with a p-value of <0.1 in univariable analysis and performed hierarchical regression, entering variables in blocks of demographics, treatment and disease-related variables prior to assessing the effect of multimorbidity. Age and gender were controlled for in every model. Adjusted R^2 was used to determine the additional variation explained by each block of variables entered. The final models retained variables that significantly improved the fit.

The appropriate assumptions for each statistical test were met. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 24.

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RESULTS

Baseline characteristics

At time of database extraction in February 2018, the ASRI cohort contained 734 patients, from 12 Rheumatology centres representing all geographical regions of Ireland. Seventy-seven percent (n=536) of the patients in ASRI are male, with a mean (SD) age of 45 (12) years and a median (IQR) disease duration of 16 (9 to 27) years. The baseline demographic and clinical characteristics of the ASRI cohort are outlined in table 1.

Multimorbidity profile of ASRI cohort

Fifty-five percent of the cohort (n=403) is multimorbid i.e. at least one chronic condition in addition to axSpA: 25% (n=180) has 1 additional chronic condition, 16% (n=118) has 2 additional chronic conditions, 8% (n=57) has 3 additional chronic conditions and 7% (n=48) has 4 or more additional chronic conditions.

The most prevalent chronic condition is obesity, affecting 27% (n=192) of the population, followed by hypertension (n=155, 21%), hyperlipidaemia (n=119, 16%) and depression (n=76, 10%). Thirty percent (n=222) of patients have cardiovascular comorbidity i.e. at least one of IHD, cerebrovascular disease, hypertension, hypercholesterolaemia. Remaining conditions are outlined in figure 1.

Thirty-nine patients (5.3%) report a prior diagnosis or had a diagnosis recorded in the medical record of osteoporosis. Only 19.5% (n=143) had previously had a DXA, of which 95 hip and 94 spine DXA results were available (results of DXAs performed in private facilities or primary care were not universally available): 58% had low BMD at the hip (43% osteopenia, 15% osteoporosis) and 50% had low BMD at the spine (33% osteopenia, 17% osteoporosis).

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Comparison of multimorbid and non-multimorbid patients

Demographics/clinical characteristics

Multimorbid patients are older, with longer disease duration and longer delay to diagnosis than axSpA-only patients (see table 1). Multimorbid patients have similar CRP and ESR to the axSpA-only cohort. Gender and HLA-B27 status have no effect on the presence or absence of multimorbidity. The prevalence of psoriasis is higher in multimorbid patients than axSpA-only patients (21% versus 15%, p=0.02). Uveitis and IBD are equally prevalent in both groups.

Impact of multimorbidity on disease outcomes

Across all disease outcome measures, multimorbid patients have more severe disease than patients with axSpA-only (see table 1). Disease outcome measures also correlate with the burden of multimorbidity, which is measured by the number of additional chronic conditions: as the burden of multimorbidity increases, BASDAI scores worsen (see table 2 for all outcomes measures).

The cohort was subsequently compared in 3 groups: (a) axSpA-only, (b) multimorbid with 1 additional chronic condition, (c) multimorbid with 2 or more additional chronic conditions. Disease outcome measures were all significantly higher in patients with multimorbidity compared to patients with axSpA-only, regardless of the number of chronic conditions (see table 3). However, when comparing within the patients with multimorbidity, only BASMI, BASFI and HAQ were significantly higher in patients with 2 or more additional conditions compared to patients with 1 additional condition. There was no difference in BASDAI and ASQoL scores between the multimorbid cohort with 2 or more additional conditions and 1 additional condition (see table 3; ANOVA analysis presented in supplementary table 1).

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Regression analysis

Multimorbid versus non-multimorbid

In adjusted analyses (see table 4), when compared to patients with axSpA only, being multimorbid is associated with a higher BASDAI of 0.7 (95% CI 0.34 to 1.05), BASMI of 0.45 (95% CI 0.09 to 0.80), BASFI of 0.5 (95% CI 0.23 to 0.78), HAQ of 0.07 (95% CI 0.00 to 0.13) and ASQoL of 0.87 (95% CI 0.28 to 1.46).

Severity of multimorbidity

In separate models investigating the association between severity of multimorbidity and outcomes (see table 4), the presence of each additional condition was associated with a higher BASDAI of 0.23 (95% CI 0.09 to 0.37), BASMI of 0.20 (95% CI 0.05 to 0.34), ASQoL of 0.25 (95% CI 0.02 to 0.49), HAQ of 0.03 (95% CI 0.01 to 0.06) and BASFI of 0.21 (95% CI 0.10 to 0.32).

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DISCUSSION

There is growing interest in multimorbidity. Multimorbid patients have complex needs, requiring cohesive individualised patient-centred strategies, rather than the traditional disease-focused model of care, in order to meet the needs of a rapidly expanding population (8). The negative consequences of multimorbidity are well-outlined in the general population (12, 13, 15), but much less is known about its impact in axSpA patients. Our study found multimorbidity is common in axSpA patients, affecting over half (55%) of this large well-characterised cohort. Additionally, multimorbidity is associated with worse disease outcomes than those with axSpA alone.

The prevalence in our cohort is higher than in the general population, where the prevalence of multimorbidity is around 23% (12), although estimates vary from 13% to 95% (11, 39) depending on age-group and definition of multimorbidity used. Prevalence of multimorbidity is also higher in primary care populations than the general population (40). Musculoskeletal diseases (MSD) are common in patients with multimorbidity (16) and multimorbidity is equally prevalent in RA, affecting over 60% of patients (20), therefore it is unsurprising that multimorbidity is common in axSpA patients.

In our study, we defined the differences between multimorbid and axSpA-only patients. Multimorbid axSpA patients have longer disease duration, longer delay to diagnosis and are on average 10 years older than patients with axSpA only, a similar trend to other populations where multimorbidity increases with age (12, 41). However, with multimorbid axSpA patients averaging 50 years, younger than that seen in primary care practice populations and in RA (12, 19), multimorbidity is not exclusive to the elderly in axSpA.

A systematic review of the general population found an association between women and multimorbidity (11). However, literature is conflicting in RA, where both no gender effect (19) and

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a predominance of women in the multimorbid group (42) have been shown. Males and females are equally affected by multimorbidity in our study.

Obesity is the most common morbidity, affecting 26% of our cohort. The prevalence of hypertension (21%) and hypercholesterolaemia (16%) is lower in our study than in ASAS-COMOSPA, but frequency of ischaemic heart disease (3%) and cerebrovascular disease (2%) is similarly low (23). Cardiovascular morbidity is common (30%) in multimorbid patients in our study, reflecting international trends (7). Depression is prevalent in our study, affecting 10% of patients, as is alcohol excess (9%).

Obesity is not always included in multimorbidity scores, with it only counted as a chronic condition in 5 of 39 multimorbidity counts in a systematic review in 2011 (43). However, obesity was only officially recognised as a disease in 2013 (44). As it has a clear negative impact on mortality (45) and represents a growing public health challenge, it is worthy of being considered in a multimorbidity count (41), thus our decision to include it.

In ASAS-COMOSPA, osteoporosis was the most frequent co-morbidity, affecting 13% of the cohort (23). The prevalence of self-reported osteoporosis in our study is 5.3%. However, systematic screening isn't feasible in the context of a registry study. Using the DXA data available in a minority of the cohort, 17% have osteoporosis. However, this may be an overestimation of the population prevalence, as patients referred for DXA assessment likely had risk factors making a diagnosis of osteoporosis more probable, thus the true prevalence is expected to fall between 5 and 17%, closer to that reported in ASAS-COMOSPA.

The second aim of this study is to determine the association between multimorbidity and disease outcomes in axSpA. We demonstrate an association between multimorbid patients and worse disease outcomes, using both subjective and objective outcome measures. As the severity of multimorbidity increases, so too do disease outcome scores. Our results reflect the general population, where multimorbidity is associated with impaired function and worse quality of life,

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particularly if a rheumatic disease is involved (46), and RA, where multimorbid patients have more severe disease and more fatigue than patients with RA only (19, 47). Nikiphorou et al (24) similarly demonstrated that a rising comorbidity burden is associated with worse QoL in SpA patients.

However, what differentiates our study from those which focus on co-morbidity is we demonstrate that simply being multimorbid, i.e. having any additional condition to axSpA, is associated with worse outcomes compared to patients with axSpA alone. The difference in outcomes between axSpA-only and being multimorbid is more marked than the difference for each additional condition thereafter. This has potential to be a clinically useful finding, which could provide physicians with a simple method to identify patients at risk of poor outcomes.

We would like to acknowledge some limitations. Firstly, the cross-sectional design of this registry study prohibits comment on causality, therefore we can merely observe the association between multimorbidity and severe disease. Secondly, the absence of information on co-morbidities not collected within the framework of ASRI represents a potential limitation. However, our study reports the co-morbidities known to occur most commonly in SpA, as outlined in ASAS-COMOSPA (23), with the exception of infections (hepatitis B prevalence of 3.5% in SpA worldwide). In Ireland the prevalence of hepatitis B is known to be very low (<0.1%) (48), therefore it is unlikely to have influenced the results. Additionally, pulmonary disease is not collected in ASRI. However, although abnormalities on high-resolution computed-tomography imaging of the thorax are common (49), the clinical significance of these is unknown (50), therefore we are confident that not including a measure of the prevalence of pulmonary disease is unlikely to have significantly affected the prevalence of multimorbidity. Thirdly, alcohol intake is based on patients own report. It has been well established that patients tend to underestimate their alcohol consumption. All efforts were made to establish an accurate alcohol intake, but it is possible that intake was under-reported, thus under-estimating the prevalence of alcohol excess. Fourthly, our population is

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overwhelmingly Caucasian, therefore extrapolating the results of our study to other ethnicities is not possible.

However, our study has many strengths. It is a large study, with a well characterised cohort. The homogenous nature of our patients reduces variation that could be introduced from diverse backgrounds. Additionally, it contains real-life data, providing clinicians with relevant and clinically useful information. It is also novel, as the first study to examine prevalence estimates of multimorbidity in axSpA. To date, studies have primarily focused on individual comorbidities in axSpA, along with their impact on disease outcomes/management. Focusing on individual conditions takes the focus away from the patient; different conditions are considered the index disease by different clinicians, all aiming for best control of their disease of interest, without necessarily considering its impact on other diseases, potentially leading to fragmented care (8, 9). Multimorbidity brings the focus back to the patient, not the disease. Further research is needed to further delineate the impact of multimorbidity in our patients. Specifically, prospective longitudinal studies are needed to investigate the development of multimorbidity in axSpA and its impact on disease outcomes over time.

In conclusion, we have demonstrated that multimorbidity is prevalent in axSpA patients and that the presence of multimorbidity is associated with worse disease outcomes.

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ACKNOWLEDGEMENTS

This study was conducted on behalf of the steering committee of the Ankylosing Spondylitis Registry of Ireland. We would like to thank all the patients for participating in this study. We would also like to thank all the personnel in the centres who so willingly and enthusiastically contributed, and continue to contribute, data to ASRI: Blackrock Clinic, Cork University Hospital, Galway University Hospitals, Midland Regional Hospital Tullamore, Our Lady's Hospital Manorhamilton, Our Lady's Hospital Navan, St. James's Hospital, St. Vincent's University Hospital, Tallaght University Hospital, University Hospital Kerry, University Hospital Limerick, University Hospital Waterford.

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REFERENCES

1. The 2015 Ageing Report: Economic and budgetary projections for the 28 EU Member States (2013-2060). Luxembourg: Publications Office of the European Union; 2015. Report No.: 978-92-79-44746-4 (online)ISBN 978-92-79-44747-1 (print) Contract No.: Document Number|.
2. Arias E, Heron M, Xu J. United States Life Tables, 2013. Natl Vital Stat Rep 2017;66:1-64
3. Rechel B, Grundy E, Robine JM, Cylus J, Mackenbach JP, Knai C, et al. Ageing in the European Union. Lancet 2013;381:1312-22
4. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet 2009;374:1196-208
5. Fries JF. The compression of morbidity. Milbank Mem Fund Q Health Soc 1983;61:397-419
6. Pefoyo AJ, Bronskill SE, Gruneir A, Calzavara A, Thavorn K, Petrosyan Y, et al. The increasing burden and complexity of multimorbidity. BMC Public Health 2015;15:415
7. WHO. Global status report on noncommunicable diseases 2014. World Health Organization; 2015 [updated 2015 2015-10-05 03:00:00; cited]; Available from: http://www.who.int/nmh/publications/ncd-status-report-2014/en/.
8. Navickas R, Petric VK, Feigl AB, Seychell M. Multimorbidity: What do we know? What should we do? J Comorb 2016;6:4-11
9. Radner H, Yoshida K, Smolen JS, Solomon DH. Multimorbidity and rheumatic conditions-enhancing the concept of comorbidity. Nat Rev Rheumatol 2014;10:252-6
10. Almirall J, Fortin M. The coexistence of terms to describe the presence of multiple concurrent diseases. J Comorb 2013;3:4-9
11. Violan C, Foguet-Boreu Q, Flores-Mateo G, Salisbury C, Blom J, Freitag M, et al. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. PLoS One 2014;9:e102149
12. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012;380:37-43
13. Menotti A, Mulder I, Nissinen A, Giampaoli S, Feskens EJ, Kromhout D. Prevalence of morbidity and multimorbidity in elderly male populations and their impact on 10-year all-cause mortality: The FINE study (Finland, Italy, Netherlands, Elderly). J Clin Epidemiol 2001;54:680-6
14. McDaid O, Hanly MJ, Richardson K, Kee F, Kenny RA, Savva GM. The effect of multiple chronic conditions on self-rated health, disability and quality of life among the older populations of Northern Ireland and the Republic of Ireland: a comparison of two nationally representative cross-sectional surveys. BMJ open 2013;3:e002571
15. Cassell A, Edwards D, Harshfield A, Rhodes K, Brimicombe J, Payne R, et al. The epidemiology of multimorbidity in primary care: a retrospective cohort study. Br J Gen Pract 2018;68:e245-e251
16. Simoes D, Araujo FA, Severo M, Monjardino T, Cruz I, Carmona L, et al. Patterns and Consequences of Multimorbidity in the General Population: There is No Chronic Disease Management Without Rheumatic Disease Management. Arthritis Care Res (Hoboken) 2017;69:12-20
17. van der Zee-Neuen A, Putrik P, Ramiro S, Keszei A, de Bie R, Chorus A, et al. Impact of Chronic Diseases and Multimorbidity on Health and Health Care Costs: The Additional Role of Musculoskeletal Disorders. Arthritis Care Res (Hoboken) 2016;68:1823-31
18. Duffield SJ, Ellis BM, Goodson N, Walker-Bone K, Conaghan PG, Margham T, et al. The contribution of musculoskeletal disorders in multimorbidity: Implications for practice and policy. Best Pract Res Clin Rheumatol 2017;31:129-44

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19. Radner H, Yoshida K, Hmamouchi I, Dougados M, Smolen JS, Solomon DH. Treatment Patterns of Multimorbid Patients with Rheumatoid Arthritis: Results from an International Cross-sectional Study. J Rheumatol 2015;42:1099-104
20. Radner H, Yoshida K, Mjaavatten MD, Aletaha D, Frits M, Lu B, et al. Development of a multimorbidity index: Impact on quality of life using a rheumatoid arthritis cohort. Semin Arthritis Rheum 2015;45:167-73
21. Radner H, Yoshida K, Frits M, Iannaccone C, Shadick NA, Weinblatt M, et al. The impact of multimorbidity status on treatment response in rheumatoid arthritis patients initiating disease-modifying anti-rheumatic drugs. Rheumatology (Oxford) 2015;54:2076-84
22. Walsh JA, Song X, Kim G, Park Y. Evaluation of the comorbidity burden in patients with ankylosing spondylitis using a large US administrative claims data set. Clin Rheumatol 2018;37:1869-78
23. Molto A, Etcheto A, van der Heijde D, Landewe R, van den Bosch F, Bautista Molano W, et al. Prevalence of comorbidities and evaluation of their screening in spondyloarthritis: results of the international cross-sectional ASAS-COMOSPA study. Ann Rheum Dis 2016;75:1016-23
24. Nikiphorou E, Ramiro S, van der Heijde D, Norton S, Molto A, Dougados M, et al. Association of Comorbidities in Spondyloarthritis associate with poor function, work disability and quality of life: Results from the ASAS-COMOSPA study. Arthritis Care Res (Hoboken) 2018;70:1257-1262.
25. Haroon NN, Paterson JM, Li P, Inman RD, Haroon N. Patients With Ankylosing Spondylitis Have Increased Cardiovascular and Cerebrovascular Mortality: A Population-Based Study. Ann Intern Med 2015;163:409-16
26. Exarchou S, Lie E, Lindstrom U, Askling J, Forsblad-d'Elia H, Turesson C, et al. Mortality in ankylosing spondylitis: results from a nationwide population-based study. Ann Rheum Dis 2016;75:1466-72
27. Bakland G, Gran JT, Nossent JC. Increased mortality in ankylosing spondylitis is related to disease activity. Ann Rheum Dis 2011;70:1921-5
28. Ahmed N, Prior JA, Chen Y, Hayward R, Mallen CD, Hider SL. Prevalence of cardiovascular-related comorbidity in ankylosing spondylitis, psoriatic arthritis and psoriasis in primary care: a matched retrospective cohort study. Clin Rheumatol 2016;35:3069-73
29. Bremander A, Petersson IF, Bergman S, Englund M. Population-based estimates of common comorbidities and cardiovascular disease in ankylosing spondylitis. Arthritis Care Res (Hoboken) 2011;63:550-6
30. van der Heijde D, Ramiro S, Landewe R, Baraliakos X, Van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017;76:978-91
31. Health Service Executive. Alcohol Programme. 2015 [updated 2015; cited 2018 12 Nov]; Available from: https://www.hse.ie/eng/health/hl/change/alcohol/.
32. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol 1994;21:1694-8
33. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med 1993;94:646-50
34. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286-91
35. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281-5
36. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45

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37. Doward LC, Spoorenberg A, Cook SA, Whalley D, Helliwell PS, Kay LJ, et al. Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis 2003;62:20-6
38. van den Akker M, Buntinx F, Knottnerus JA. Comorbidity or multimorbidity. European Journal of General Practice 1996;2:65-70
39. Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. Lancet Public Health 2018;3:e323-e32
40. Mokraoui NM, Haggerty J, Almirall J, Fortin M. Prevalence of self-reported multimorbidity in the general population and in primary care practices: a cross-sectional study. BMC Res Notes 2016;9:314
41. Agborsangaya CB, Ngwakongnwi E, Lahtinen M, Cooke T, Johnson JA. Multimorbidity prevalence in the general population: the role of obesity in chronic disease clustering. BMC Public Health 2013;13:1161
42. Armagan B, Sari A, Erden A, Kilic L, Erdat EC, Kilickap S, et al. Starting of biological disease modifying antirheumatic drugs may be postponed in rheumatoid arthritis patients with multimorbidity: Single center real life results. Medicine (Baltimore) 2018;97:e9930
43. Diederichs C, Berger K, Bartels DB. The measurement of multiple chronic diseases--a systematic review on existing multimorbidity indices. J Gerontol A Biol Sci Med Sci 2011;66:301-11
44. Kyle TK, Dhurandhar EJ, Allison DB. Regarding Obesity as a Disease: Evolving Policies and Their Implications. Endocrinol Metab Clin North Am 2016;45:511-20
45. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA 2013;309:71-82
46. Loza E, Jover JA, Rodriguez L, Carmona L. Multimorbidity: prevalence, effect on quality of life and daily functioning, and variation of this effect when one condition is a rheumatic disease. Semin Arthritis Rheum 2009;38:312-9
47. Tournadre A, Pereira B, Gossec L, Soubrier M, Dougados M. Impact of comorbidities on fatigue in rheumatoid arthritis patients: results from a nurse-led program for comorbidities management (COMEDRA). Joint Bone Spine 2018;
48. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet 2015;386:1546-55
49. El Maghraoui A, Dehhaoui M. Prevalence and characteristics of lung involvement on high resolution computed tomography in patients with ankylosing spondylitis: a systematic review. Pulm Med 2012;2012:965956
50. Ozdemir O, Gulsun Akpinar M, Inanici F, Hascelik HZ. Pulmonary abnormalities on high-resolution computed tomography in ankylosing spondylitis: relationship to disease duration and pulmonary function testing. Rheumatol Int 2012;32:2031-6

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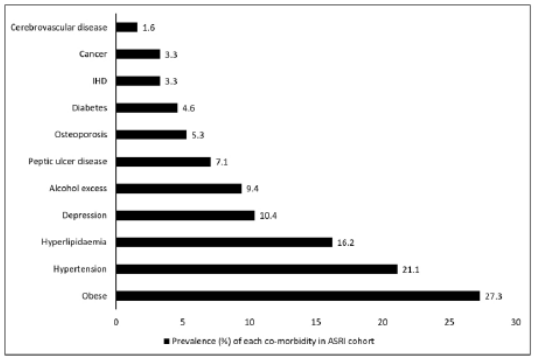

Figure 1: Prevalence of co-morbidities in ASRI cohort, ranked from least to most common. IHD, ischaemic heart disease.

Prevalence of co-morbidities in ASRI, ranked from least to most common.

203x114mm (240 x 240 DPI)

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Table 1: Baseline demographic and clinical characteristics of cohort according to multimorbidity status

	Whole population (n=734)	AxSpA only (n=331)	Multimorbid (n=403)	P value†
Males	563 (76.7)	251 (75.8)	312 (77.4)	0.61
Age, years	45 (12.4)	39.6 (10.7)	49.5 (12)	**<0.01**
Disease duration, years	16 (9, 27)	13 (7, 20)	20 (12, 32)	**<0.01**
Delay to diagnosis, years	6 (2, 11)	5 (2,10)	7 (3, 13)	**<0.01**
Caucasian	708 (96.5)	311 (94)	397 (98.5)	**<0.01**
mNY criteria	570 (77.7)	247 (74.6)	323 (80.1)	0.07
ASAS criteria	690 (94)	313 (94.6)	377 (93.5)	0.57
HLA-B27 positive*	502 (91.1)	238 (91.9)	264 (90.4)	0.54
Unemployed¶	166 (22.6)	60 (18.1)	106 (26.3)	**0.01**
Smoker				
• Current smoker	219 (29.8)	106 (32)	113 (28)	**0.02**
• Ex-smoker	207 (28.2)	76 (23)	131 (32.5)	**0.02**
BMD , T-score				
• Hip	-1.2 (1.1)	-1.3 (0.8)	-1.1 (-2, -0.1)	0.38
• Spine	-0.7 (1.9)	-0.9 (1.2)	-0.7 (-2.3, 1.2)	0.30
Waist circumference, cm	95 (85, 104)	88 (81, 96)	101 (91, 110)	**<0.01**
ESR§, mm/h	10 (5, 20)	10 (5, 19)	11 (5, 22)	0.09
CRP§, mg/L	3 (1, 7.7)	2.5 (1, 7)	3 (1, 8)	0.18
BMI, kg/m²	26.6 (23.9, 30.3)	24.7 (22.9, 27)	29.5 (26, 32.9)	**<0.01**
Extra-spinal manifestations				

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• Peripheral arthritis	239 (33.3)	89 (27.4)	150 (38.2)	**<0.01**
• Enthesitis	125 (17.5)	49 (15.2)	76 (19.3)	0.14
• Uveitis	256 (35.7)	109 (33.6)	147 (37.4)	0.30
• Dactylitis	50 (7)	17 (5.2)	33 (8.4)	0.10
• Psoriasis	131 (18.2)	47 (14.5)	84 (21.3)	**0.02**
• IBD	71 (9.9)	26 (8)	45 (11.2)	0.13
Treatment history				
• Current NSAIDs	373 (50.8)	155 (46.8)	218 (54.1)	0.05
• Current sulfasalazine	29 (4)	13 (3.9)	16 (4)	0.14
• Current methotrexate	47 (6.4)	11 (3.3)	36 (8.9)	0.25
• Lifetime TNFi use	512 (69.8)	229 (69.2)	283 (70.2)	0.76
• Current TNFi	456 (62.1)	207 (62.5)	249 (61.8)	0.84
Disease severity				
• ASQoL, 0-18	6 (1, 12)	3 (0, 9)	7 (3, 13)	**<0.01**
• HAQ, 0-3	0.4 (0, 0.9)	0.3 (0, 0.6)	0.63 (0.25, 1)	**<0.01**
• BASDAI, 0-10	3.9 (2, 5.8)	3 (1.5, 5.4)	4.4 (2.6, 6.2)	**<0.01**
• BASFI, 0-10	3.3 (1.3, 5.6)	2 (0.7, 4.2)	4.5 (2.2, 6.5)	**<0.01**
• BASMI, 0-10	3 (1, 6)	2 (1, 4)	4 (2, 7)	**<0.01**

Data are mean (SD), median (25th quartile, 75th quartile) or n (%). Significant values in bold. * HLA-B27 status unknown in n=183 patients. ¶Patients within employment age but unemployed. † Comparison between axSpA-only and multimorbid patient groups (Independent T-tests for continuous variables, Chi-square analysis for categorical variables). Most recent BMD results. §Refers to values at time of recruitment. ASAS: Assessment of SpondyloArthritis Society; ASQoL: Ankylosing Spondylitis Quality of Life Index; AxSpA: axial spondyloarthropathy; BMD: bone mineral density; HAQ: Health Assessment Questionnaire; HLA: Human leucocyte antigen; IBD, inflammatory bowel disease; IBD: Inflammatory Bowel Disease; mNY: modified New York; NSAIDs: Non-steroidal anti-inflammatory drugs; TNFi: TNF inhibitor.

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Table 2: Relationship between increasing multimorbidity and disease outcome measures.

	Increasing multimorbidity	BASDAI	BASFI	BASMI	ASQoL	HAQ
	Rho	***Rho***	***Rho***	***Rho***	***Rho***	***Rho***
	P	**P**	**P**	**P**	**P**	**P**
	n	**n**	**n**	**n**	**n**	**n**
Increasing burden of multimorbidity	...	0.21	0.36	0.35	0.23	0.27
	...	<0.01	<0.01	<0.01	<0.01	<0.01
	...	725	734	713	732	731

Rho: Spearman's correlation coefficient; P: P value; N: number of patients. ASQoL: Ankylosing Spondylitis Quality of Life index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI; Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; HAQ: Health Assessment Questionnaire

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Table 3: Comparison of disease outcome scores for patients with axSpA only, multimorbid patients with 1 additional condition and multimorbid patients with 2 or more conditions.

					Tukey's HSD Comparisons†	
Disease outcome	**Group**	**N**	**Mean**	**SD**	**axSpA only**	**1 additional condition**
BASDAI	axSpA only	326	3.5	2.4	...	...
	1 additional condition	178	4.2	2.4	<0.01*	...
	≥ 2 additional conditions	221	4.7	2.3	<0.01*	0.16
BASFI	axSpA only	331	2.7	2.4	...	...
	1 additional condition	180	4.0	2.6	<0.01*	...
	≥ 2 additional conditions	223	4.8	2.6	<0.01*	<0.01*
BASMI	axSpA only	322	2.7	2.3	...	...
	1 additional condition	173	3.6	2.5	<0.01*	...
	≥ 2 additional conditions	218	4.8	2.6	<0.01*	<0.01*
ASQoL	axSpA only	330	5.2	5.3	...	...
	1 additional condition	179	7.5	5.5	<0.01*	...
	≥ 2 additional conditions	223	7.9	5.7	<0.01*	0.76
HAQ	axSpA only	330	0.39	0.45	...	...
	1 additional condition	180	0.57	0.51	<0.01*	...
	≥ 2 additional conditions	221	0.72	0.59	<0.01*	0.01*

†P values presented. * Denotes significant difference. ASQoL: Ankylosing Spondylitis Quality of Life index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; HAQ: Health Assessment Questionnaire; HSD: Honestly Significant Difference; N: number of patients; SD: standard deviation. ... denotes duplicate cells left blank.

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Table 4: Adjusted analyses of association between disease outcome measures and (1) presence of multimorbidity and (2) severity of multimorbidity

	Outcome variables				
	BASDAI	BASFI	BASMI	ASQoL	HAQ
(1)	ß (95% CI)	ß (95% CI)	ß (95% CI)	ß (95% CI)	ß (95% CI)
Independent variables					
Age	0.01 (-0.01 to 0.02)	0.05 (0.04 to 0.06)	0.09 (0.08 to 0.11)	-0.01 (-0.03 to 0.02)	0.01 (0.00 to 0.01)
Gender (male v female)	-0.94 (-1.32 to -0.56)	-0.19 (-0.49 to 0.11)	0.50 (0.11 to 0.89)	-0.55 (-1.10 to 0.09)	-0.07 (-0.15 to -0.01)
Multimorbid (yes v no)	0.70 (0.34 to 1.05)	0.50 (0.23 to 0.78)	0.45 (0.09 to 0.80)	0.87 (0.28 to 1.46)	0.07 (0.00 to 0.13)
BASDAI	§	0.68 (0.62 to 0.73)	§	1.64 (1.52 to 1.76)	0.12 (0.10 to 0.13)
Unemployed (yes v no)	1.62 (1.23 to 2.00)	0.84 (0.52 to 1.15)	1.48 (1.09 to 1.87)	1.39 (0.72 to 2.05)	0.21 (0.13 to 0.28)
Current/past smoker (yes v no)	0.39 (0.07 to 0.71)	0.31 (0.06 to 0.57)	‡	‡	‡
NSAIDs use (yes v no)	1.04 (0.72 to 1.36)	‡	†	‡	‡
ESR	‡	‡	0.03 (0.02 to 0.04)	‡	‡

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(2)	BASDAI ß (95% CI)	BASFI ß (95% CI)	BASMI ß (95% CI)	ASQoL ß (95% CI)	HAQ ß (95% CI)
Independent variables					
Age	0.01 (-0.01 to 0.02)	0.05 (0.04 to 0.06)	0.09 (0.07 to 0.11)	-0.01 (-0.03 to 0.02)	0.01 (0.00 to 0.01)
Gender (male v female)	-0.89 (-1.26 to -0.49)	-0.07 (-0.37 to 0.23)	0.64 (0.23 to 1.04)	-0.35 (-0.99 to 0.30)	-0.04 (-0.11 to 0.04)
Worsening multimorbidity	0.23 (0.09 to 0.37)	0.21 (0.10 to 0.32)	0.20 (0.05 to 0.34)	0.25 (0.02 to 0.49)	0.03 (0.01 to 0.06)
BASDAI	§	0.73 (0.67 to 0.78)	§	1.72 (1.61 to 1.84)	0.12 (0.11 to 0.14)
Delay to diagnosis	‡	‡			-0.01 (-0.01 to -0.00)
Unemployed (yes v no)	1.68 (1.29 to 2.07)	†	†	†	†
Current/past smoker (yes v no)	0.38 (0.05 to 0.71)	0.58 (0.20 to 0.96)	‡	‡	‡
NSAIDs use (yes v no)	1.11 (0.79 to 1.44)	‡	‡	‡	‡
ESR	‡	‡	0.03 (0.02 to 0.04)	‡	0.00 (0.00 to 0.01)
IBD	0.74 (0.19 to 1.29)	‡	‡	‡	‡

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Variables tested in univariable regression: age, gender, unemployed, delay to diagnosis, current or past smoker, enthesitis, arthritis, dactylitis, uveitis, IBD, psoriasis, CRP, ESR, multimorbid, HLA-B27 positivity, NSAIDs use, csDMARD use, current TNFi use, lifetime history of TNFi use. Variables not included in the above table were not significant in any final model. Every model controlled for age and gender. † P > 0.1 in univariable analysis. ‡ P > 0.05 in multivariable analysis. §: not assessed. ASQoL: Ankylosing Spondylitis Quality of Life score; ß: regression coefficient; CI: confidence interval; IBD: inflammatory bowel disease; MRI: magnetic resonance imaging.

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Clinical Rheumatology
https://doi.org/10.1007/s10067-019-04876-9

ORIGINAL ARTICLE

Calcaneal quantitative ultrasound has a role in out ruling low bone mineral density in axial spondyloarthropathy

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Received: 8 November 2019 / Revised: 8 November 2019 / Accepted: 28 November 2019
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Abstract

Objective The aim of this study was to investigate the role of quantitative ultrasound (QUS) of the calcaneus in screening for osteoporosis in adults with axial spondyloarthropathy (axSpA).

Method Postmenopausal women and men over 50 years with axSpA were recruited for this observational cross-sectional study. Dual-energy x-ray absorptiometry (DXA) assessed bone mineral density (BMD) of the spine and hip. QUS of the calcaneus produced broadband ultrasound attenuation (BUA), speed of sound (SOS), stiffness index (SI), and T-scores. Receiver-operating characteristics (ROC) curve analysis determined the ability of QUS to discriminate between low and normal BMD. Thresholds were identified to (1) out rule low BMD, (2) identify osteoporosis, and (3) identify low BMD. The number of DXAs which could be avoided using this approach was calculated.

Results 56 participants were analyzed. BUA, SI, and T-score QUS parameters correlated with BMD by DXA; SOS did not. All QUS parameters had the ability to discriminate between low and normal BMD (area under the curve varied from 0.695 to 0.779). QUS identified individuals without low BMD with 90% confidence, with BUA performing best (sensitivity 93%, negative predictive value 86%). Using QUS as a triage tool, up to 27% of DXA assessments could have been avoided. QUS could not confidently identify individuals with osteoporosis.

Conclusions QUS of the calcaneus confidently out ruled low BMD in individuals with axSpA, reducing the need for onward DXA referral by up to 27%. QUS is promising as a non-invasive triage tool in the assessment of osteoporosis in adults with axSpA.

Key Points
- *Osteoporosis is common in axial spondyloarthropathy (SpA), but evaluation of bone health is suboptimal in this population.*
- *Quantitative ultrasound (QUS) of the calcaneus can out rule low bone mineral density in individuals with axial SpA, reducing the need for DXA assessment.*
- *QUS is a promising non-invasive triage tool in the assessment of bone health in axial SpA.*

Keywords Bone density · Diagnostic screening programs · Osteoporosis · Spondyloarthropathies · Ultrasonography

Data from this manuscript has been published as an abstract in conference proceedings: Fitzgerald G, Anachebe T, Mullan R, Kane D, McCarroll K, O'Shea F. Quantitative Ultrasound of the Calcaneus Has a Role to Play in Detecting Low Bone Mineral Density in Axial Spondyloarthropathy Patients [abstract]. Arthritis Rheumatol. 2018; 70 (suppl 10). https://acrabstracts.org/abstract/quantitative-ultrasound-of-the-calcaneus-has-a-role-to-play-in-detecting-low-bone-mineral-density-in-axial-spondyloarthropathy-patients/. Accessed October 28, 2019.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10067-019-04876-9) contains supplementary material, which is available to authorized users.

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Introduction

Osteoporosis occurs commonly in individuals with axial spondyloarthropathy (axSpA) [1]. The prevalence of fractures in axSpA is increased compared to controls [2], and the potential for devastating neurological outcomes from vertebral fractures is significantly increased [3]. Despite this, less than a third of rheumatologists assess for osteoporosis as part of their routine management of adults with AS [4]. In a recent study, just under 20% of adults with axSpA had ever had a DXA assessment of their bone mineral density (BMD) [5]. This suggests that the systematic assessment of bone health in axSpA is suboptimal.

Dual-energy x-ray absorptiometry (DXA) is the gold standard for assessing bone mineral density (BMD) and is an important tool in the subsequent diagnosis or exclusion of osteoporosis [6]. It is also the recommended method to monitor changes in BMD [6]. However, as the general population continues to age [7], the demand for a comprehensive assessment of bone health, including DXA assessment, is growing. This can result in reduced access to DXA, with long waiting times.

A triage tool to identify an individual's risk of having osteoporosis could reduce the burden on DXA by risk-stratifying individuals. DXA assessment could be delayed if clinicians could confidently categorize an individual as low risk for having low BMD. Individuals at very high risk of having osteoporosis could also be identified, allowing treatment to be commenced prior to DXA assessment. This would ensure appropriate use of available resources, reserving DXA for individuals who require a definitive assessment of their BMD with DXA.

Quantitative ultrasound (QUS) of the calcaneus has potential as a triage tool for osteoporosis. It has many advantages over DXA: it does not contain any ionizing radiation, and it is portable and non-invasive. QUS generates two parameters: speed of sound (SOS) and broadband ultrasound attenuation (BUA) [8]. SOS refers to the division of transmission time of the sound waves by the length of the body part studied, expressed as meter per second (m/s) [8]. BUA refers to the slope between attenuation of sound signals and its frequency, measured in dB/Hz [8]. The stiffness index (SI) is a composite measure of SOS and BUA, which is useful in determining people with low bone health [9]. The calcaneus is the only site recognized by the International Society of Clinical Densitometry (ISCD) suitable for QUS assessment of bone health [10]. The use of the same T-score cutoffs as DXA to quantify normal BMD, osteopenia, and osteoporosis is not recommended by the ISCD as they employ different techniques to assess bone health [6]. Instead, device-specific cutoffs are needed [8].

The lack of diagnostic criteria and lack of evidence that treatment based on QUS parameters is effective prohibits the replacement of DXA with QUS [11]. However, using QUS as a triage tool would reduce the demand on DXA, by limiting the number of individuals who need to undergo the reference test. QUS of the calcaneus has been shown to predict fractures in postmenopausal women and men over 65 years [6, 12, 13]. A systematic review demonstrated that QUS of the calcaneus was potentially useful as a prescreening tool in the assessment of osteoporosis, using device-specific thresholds [11]. Speden et al. [14] investigated the role of QUS in 23 women with axSpA and found no consistent correlation between QUS and BMD of the hip or spine. However, Jansen et al. [15] demonstrated that in AS, QUS performed similarly to DXA in detecting individuals with osteoporosis-related fractures.

The role of QUS in screening for osteoporosis in adults with axSpA has not been examined. Therefore, the aim of this study was to investigate the use of QUS of the calcaneus as a triage tool when screening for osteoporosis in adults with axSpA.

Materials and methods

Study design, setting, and population

This was an observational, cross-sectional, twin-center study, which took place between April 2017 and January 2018. The study was prospectively approved by the Tallaght University Hospital/St. James's Hospital Research Ethics Committee, in Dublin, Ireland, and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Participants were consecutively recruited from dedicated spondylitis and general rheumatology clinics in St. James's Hospital and Tallaght University Hospital, Dublin, Ireland. Participants were eligible if they fulfilled the Assessment of SpondyloArthritis Society (ASAS) criteria for axSpA [16] and the inclusion criteria for the WHO classification of osteoporosis (premenopausal women and men over the age of 50 years) [17]. Adults were excluded if they were premenopausal (women), under the age of 50 years (men), had a history of cognitive impairment which precluded informed consent, or had a history of current or past treatment with osteoporosis treatment, defined as antiresorptive medication (bisphosphonates, denosumab), anabolic medication (teriparatide), or strontium ranelate. All data collection was performed in St. James's Hospital, Dublin. Written informed consent was obtained from each participating subject.

Demographic and disease-related data collection

A detailed standardized assessment was performed on all participants, which collected data on demographics (gender, age, ethnicity, smoking status (never, past, current), alcohol consumption), disease characteristics (symptom duration, age at diagnosis, extraarticular manifestations, spondyloarthropathy

(SpA) features, axSpA treatment history), and osteoporosis history (prior DXA assessment (yes/no), osteoporosis risk factors, fragility fracture history). A trained investigator performed a physical examination according to a standardized technique [18], comprising tragus-to-wall, cervical rotation, modified Schober's test, lateral flexion, intermalleolar distance, chest expansion, height (measured to the nearest 0.1 cm), and weight (in kilograms (kg)). Body mass index (BMI), expressed in kg/m^2, was defined as body weight divided by square of body height. Blood samples were analyzed for human leucocyte antigen (HLA) B-27 antigen and reported as positive or negative.

BMD assessment

DXA

All BMD assessments were performed by trained radiographers in St. James's Hospital, on a Hologic Horizon A DXA scanner, with the patient in supine position. Lumbar spine BMD was measured in posteroanterior (PA) (L1–4) and lateral (L2–4) projections. Quality control and calibration were performed in accordance with international recommendations [10]. BMD was expressed as g/cm^2. The NHANES III data was used as reference for hip T-scores. The manufacturer's database was used as the reference standard to calculate PA and lateral lumbar spine T-scores, in line with ISCD positions [6]. BMD was categorized according to the World Health Organization (WHO) as normal if T-score > = − 1, osteopenia if between − 1 and − 2.5 and osteoporosis if < = − 2.5 [17].

QUS

QUS of the right calcaneus was performed using the General Healthcare (GE) Lunar Achilles InSight Densitometer. Daily calibration was performed, in accordance with the manufacturer's instructions [19]. The following parameters were obtained for each individual: SOS, BUA, SI, and T-score.

Disease outcome measures

The following patient-reported outcome measures were collected:

- Bath AS Disease Activity Index (BASDAI) [20]
- Bath AS Functional Index (BASFI) [21]
- AS Quality of Life (ASQoL) [22]
- Health Assessment Questionnaire (HAQ) [23].

Bath AS Metrology Index (BASMI) was calculated using the measurements taken during the physical assessment [18]. The modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) was calculated from lateral lumbar and cervical spine x-rays, assessing radiographic damage from a scale of 0–72, by two trained readers [24]. Antero-posterior pelvic x-rays were performed and read by two trained readers to grade sacroiliitis according to the modified New York criteria [25].

Statistical analysis

Descriptive statistics are presented as frequencies with percentages and mean with standard deviation (SD) or median with 25th and 75th percentiles, as appropriate, for categorical and continuous variables, respectively. Relationships between continuous variables were assessed using Pearson's correlation coefficients (r), to determine the strength and direction of relationships between QUS parameters and BMD at each site.

Receiver-operating characteristics (ROC) curve analysis was used to determine the ability of each parameter of QUS (SOS, BUA, SI, T-score) to discriminate between (1) osteoporosis and normal BMD and (2) low and normal BMD, at the PA spine, lateral spine, total hip, femoral neck, and hip/spine combined. Data is presented as area under the curve (AUC), with 95% confidence intervals (CI). The difference between the AUC for the QUS and BMD by DXA was tested using a two-sided test, with a p value of < 0.05 considered significant. Any parameters without significant discriminative ability were excluded from further analysis.

Using the ROC analysis, we aimed to identify three separate thresholds:

1. An upper QUS threshold measurement, *above* which there was a 90% certainty, or sensitivity, that a participant *did not have low BMD*, thus, not requiring DXA assessment. A high sensitivity of 90% was chosen in line with ISCD recommendations [26], to reduce the number of participants wrongly classified as low risk of having low BMD, i.e., false negatives.
2. A lower QUS threshold measurement, *below* which there was a 90% certainty, or specificity, that a participant *had osteoporosis*. Although participants with QUS measurements below this threshold would require onward referral for DXA assessment to establish a baseline BMD, they could be considered for treatment prior to DXA assessment, thus reducing delays. A high specificity was chosen to reduce the risk of participants mistakenly being classified as osteoporosis (false positive).
3. A QUS threshold measurement, *below* which there was a 90% certainty, or specificity, that a participant *had low BMD*. A high specificity was chosen to reduce the risk of participants mistakenly being classified as low BMD (false positive). Although individuals in this group would require DXA assessment before commencing pharmacological treatment, non-pharmacological measures to improve bone health could be employed while awaiting DXA.

Using these threshold values, we subsequently calculated positive predictive values (PPV) and negative predictive values (NPV). In individuals without low BMD, the number of DXAs that could have been avoided and the number of participants which would have been misclassified using this approach were calculated [11]. IBM SPSS version 24 was used for statistical analysis.

Results

Participant characteristics

Fiftysix participants were included in this study (see Fig. 1 in Electronic Supplementary Material). Table 1 outlines the baseline demographic and clinical characteristics of the cohort, of whom 77% were male and the average (SD) age was 58 (7.2) years. Up to 54% ($n = 30$) of the cohort had low BMD on DXA affecting at least one site. The prevalence of low BMD (T-score < -1.0) was 13% ($n = 7$) at PA spine, 43% ($n = 24$) at lateral spine, 14% ($n = 8$) at total hip, and 29% ($n = 16$) at femoral neck. The prevalence of osteoporosis (T-score ≤ -2.5) was < 1% ($n = 1$) at PA spine, 14% ($n = 8$) at lateral spine, and 0% ($n = 0$) at the hip.

Correlation analysis between QUS parameters and BMD

The mean and standard deviation for each QUS parameter is outlined in Table 1. BUA correlated significantly with BMD at the PA spine, lateral spine, and femoral neck; SI correlated with BMD at the PA spine, lateral spine, and femoral neck; T-score correlated with PA spine and femoral neck; SOS did not correlate with BMD at any site (see Table 2).

ROC curve analysis: discriminant ability of each QUS parameter to detect (1) low BMD, (2) osteoporosis, and (3) vertebral fractures

Low BMD

ROC analysis was used to determine which QUS parameters were able to discriminate between participants with and without low BMD by DXA (see Fig. 1). All QUS parameters had the ability to discriminate between a diagnosis of low BMD in any site and normal BMD, with the AUC varying from 0.695 to 0.779 (see Table 3). The discriminative ability of all QUS parameters at each individual DXA site is outlined in Table 3; none of the QUS parameters had the ability to identify cases of low BMD at total hip or PA spine.

Table 1 Baseline demographic and clinical characteristics for cohort

Variable	Whole population ($n = 56$)
Male	43 (77)
Age, *years*	58.0 (7.2)
Caucasian	54 (96)
Disease duration, *years*	32.4 (12.5)
Delay to diagnosis, *years*	8.0 (10.6)
Smoking status	
Current	14 (25)
Past	25 (45)
Never	17 (30)
HLA-B27 positive	42 (78)
BMI, kg/m^2	28.4 (4.7)
mNY criteria	53 (95)
Current biologic use	28 (50)
Disease severity[a]	
BASMI	5.4 (4.0, 6.4)
BASDAI	3.9 (2.3, 5.8)
BASFI	4.7 (2.6, 6.6)
ASQoL	7.0 (3.5, 12.0)
HAQ	0.63 (0.3, 1.3)
mSASSS	26.5 (7.8, 58.8)
QUS parameters	
SOS (m/s)	1554.4 (43.5)
BUA (dB/MHz)	111.4 (14.5)
SI	89.4 (17.3)
T-score	−0.8 (1.3)
BMD by DXA, g/cm^2	
PA spine	1.13 (0.21)
Lateral spine	0.74 (0.15)
Femoral neck	0.79 (0.11)
Total hip	0.95 (0.11)

Mean (SD) or *n* (%), unless otherwise stated. [a] Median (25th, 75th percentiles); ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BMI, body mass index; BUA, broadband ultrasound attenuation; DXA, dual-energy x-ray absorptiometry; HAQ, health assessment questionnaire; HLA, human leucocyte antigen; mNY, modified New York; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; PA, posterior-anterior; QUS, quantitative ultrasound; SD, standard deviation; SI, stiffness index; SOS, speed of sound

Osteoporosis and vertebral fractures

None of the QUS parameters were able to discriminate between osteoporosis and controls or between vertebral fractures and controls ($p > 0.05$ for AUC). However, the number of cases of osteoporosis ($n = 8$) and vertebral fractures ($n = 3$) in this cohort was small.

Table 2 Correlation matrix, demonstrating associations between quantitative ultrasound parameters and bone mineral density

BMD site[a]	QUS parameters			
	BUA	*SOS*	*SI*	*T-score*
PA spine BMD	**0.503***	0.203	**0.418***	**0.407***
Lateral spine BMD	**0.349***	0.151	**0.296***	0.273
Femoral neck	**0.515***	0.069	**0.329***	**0.312***
Total hip	**0.482***	0.016	0.271	0.260

*Denotes $p < 0.05$. [a] Measured by DXA. Values presented are Pearson correlation coefficient (r). Significant values highlighted in bold. BUA, broadband ultrasound attenuation; PA, posterior-anterior; SI, stiffness index; SOS, speed of sound

Threshold values to out rule low BMD

The ability of QUS to out rule low BMD at any site (BUA, SOS, SI, T-score), lateral spine (BUA, SI, T-score), and femoral neck (BUA and SI) was studied further. The threshold values for out ruling low BMD with 90% sensitivity are presented in Table 4, along with the corresponding specificity, PPV, and NPV. The remaining sites (total hip, PA spine) were not studied, due to the inability at these sites of QUS to discriminate between cases and controls.

Using this triage strategy, whereby participants with values above the threshold were considered low risk of having low BMD at any site and could have avoided DXA assessment, up to 27% of DXAs could have been saved, with only 4% of participants misclassified (Table 4).

Threshold values to diagnose osteoporosis

Only eight cases of osteoporosis (T-score ≤ − 2.5) were detected in this cohort. QUS parameters were unable to discriminate between osteoporosis and controls as outlined previously. Therefore, threshold values to confidently identify adults with osteoporosis without a DXA could not be established.

Threshold values to diagnose low BMD

In this approach, we aimed to identify a threshold below which participants had a high risk of being diagnosed with low BMD, using the predefined specificity of greater than 90%. The results are presented in Table 5. The number of DXAs saved was not calculated, as this subgroup would require onward DXA referral to establish a baseline BMD. However, identifying this population would allow early introduction of non-pharmacological measures to improve bone health whilst awaiting DXA.

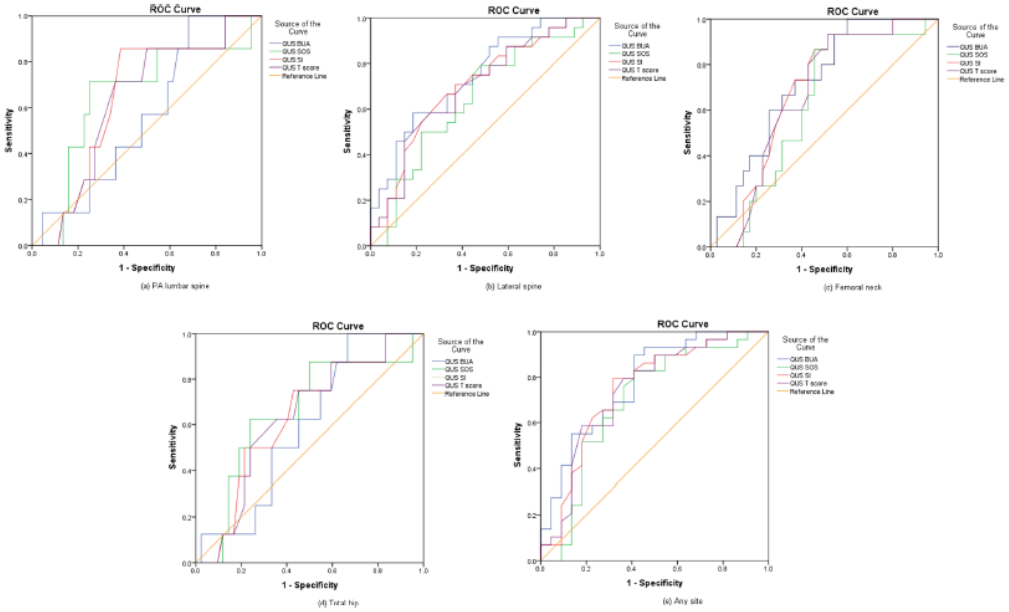

Fig. 1. Receiver operating characteristics (ROC) curves for each QUS parameter (BUA, SOS, SI, T score) as screening tools fordetecting low BMD at (**a**) PA lumbar spine, (**b**) lateral spine, (**c**) femoral neck, (**d**) total hip, and (**e**) any site

Table 3 Discriminative ability of quantitative ultrasound to diagnose low bone mineral density (BMD)

Site	Variable	AUC[a]	*P* value	95% CI[a]
Any site[a]	SOS	0.695	**0.02**	**0.538 to 0.852**
	BUA	0.779	**0.001**	**0.649 to 0.909**
	SI	0.747	**0.003**	**0.604 to 0.890**
	T-score	0.742	**0.003**	**0.599 to 0.885**
PA spine	SOS	0.653	0.20	0.425 to 0.880
	BUA	0.567	0.58	0.375 to 0.758
	SI	0.648	0.21	0.456 to 0.840
	T-score	0.633	0.26	0.439 to 0.827
Lateral spine	SOS	0.647	0.07	0.494 to 0.801
	BUA	0.746	**0.003**	**0.613 to 0.879**
	SI	0.704	**0.01**	**0.561 to 0.848**
	T-score	0.697	**0.02**	**0.552 to 0.841**
Total hip	SOS	0.658	0.16	0.449 to 0.866
	BUA	0.597	0.39	0.420 to 0.774
	SI	0.638	0.22	0.447 to 0.829
	T-score	0.635	0.23	0.446 to 0.825
Femoral neck	SOS	0.623	0.17	0.465 to 0.781
	BUA	0.718	**0.02**	**0.577 to 0.859**
	SI	0.682	**0.04**	**0.534 to 0.830**
	T-score	0.669	0.06	0.519 to 0.818

[a] Low BMD is defined as T-score < − 1 [6]. Low BMD in at least of any hip and/or any spine site measured. Significant values highlighted in bold. AUC, area under the curve; BUA, broadband ultrasound attenuation; CI, confidence interval; PA, posterior-anterior; SI, stiffness index; SOS, speed of sound

Discussion

The aim of this study was to determine the use of QUS of the calcaneus as a triage tool in the screening for osteoporosis in postmenopausal women and men over the age of 50 with axSpA. Within this study, three separate triage strategies were tested: (1) determine a threshold above which low BMD could be out ruled with 90% certainty, negating the need for a DXA assessment; (2) determine a threshold below which participants would be identified as at high risk of having osteoporosis and treatment initiation could be considered in the absence of a DXA; (3) determine a threshold below which participants could be considered at high risk of low BMD, and in the absence of other factors, non-pharmacological measures could be considered to improve bone health while awaiting DXA assessment.

Table 4 Using quantitative ultrasound (QUS) to out rule low bone mineral density (BMD), i.e. threshold above which participants have low risk of low BMD (90% sensitivity)

Site	Variable	Threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	DXAs avoided (%)[a]	Misclassification rate (%)[b]
Any site	BUA	117.65	93	55	73	86	27	4
	SOS	1591.5	93	36	66	80	20	4
	SI	106	93	32	64	78	18	4
	T-score	0.45	93	36	66	80	20	4
Lateral spine	BUA	117.65	92	44	59	86	27	4
	SI	106	92	30	52	78	18	4
	T-score	0.45	92	30	54	80	20	4
Femoral neck	BUA	114.65	93	46	42	94	34	2
	SI	93.5	93	49	44	94	36	2

[a] Calculated as TN + FN/TP + FP + FN + TN. [b] Calculated as FN/TP + FP + FN + TN. BUA, broadband ultrasound attenuation; DXA, dual-energy x-ray absorptiometry; FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; QUS, quantitative ultrasound; SI, stiffness index; SOS, speed of sound; TN, true negative; TP, true positive

Table 5 Using quantitative ultrasound (QUS) to diagnose low bone mineral density (BMD), i.e. threshold below which participants have high risk of low BMD (90% specificity)

Site	Variable	Threshold	Sensitivity (%)	Specificity (%)	PPV	NPV
Any site	BUA	102.9	41	91	78	60
	SOS	1509.5	69	91	50	53
	SI	75.5	24	91	67	57
	T-score	− 1.9	17	91	75	55
Lateral spine	BUA	100.1	29	93	78	60
	SI	72.5	21	93	71	57
	T-score	− 1.9	21	93	71	57
Femoral neck	BUA	99.0	13	91	40	71
	SI	69.5	0	91	0	68

BUA, broadband ultrasound attenuation; NPV, negative predictive value; PPV, positive predictive value; QUS, quantitative ultrasound; SI, stiffness index; SOS, speed of sound

We found that QUS of the calcaneus could identify participants without low BMD at any site (i.e., T-score < − 1 at hip and/or spine) with 90% confidence. BUA performed best among all the QUS parameters in discriminating between participants with and without low BMD, with an AUC of 0.779 for low BMD at any site. With a threshold BUA value of 117.65, a sensitivity of 93% was seen. Therefore, when BUA is greater than 117.65, there is a low likelihood of missing participants with low BMD. The corresponding specificity was 55%, indicating that many participants with normal BMD will be classified as low BMD; however, as QUS of the calcaneus is intended as a triage tool to out rule low BMD, higher sensitivity was prioritized over higher specificity to minimize false negatives. The high NPV for this threshold (86%) implies that QUS accurately identified individuals with low BMD. Therefore, we conclude that using the device-specific thresholds derived in this study, QUS could be used as a triage tool to out rule low BMD in individuals with axSpA.

We additionally investigated whether QUS could accurately identify participants with low BMD. Although thresholds were identified with high specificities (91–93%), the corresponding PPV were low (0–71%), suggesting a low probability of actually having low BMD if the QUS reading is below the threshold value. Therefore, we conclude that in this study, QUS was not a useful tool to confidently identify participants with low BMD.

In rheumatoid arthritis, QUS of the calcaneus was shown to have low ability to detect osteoporosis, but a high negative predictive value, suggesting it could have a role in screening [27]. However, a formal screening strategy has not been tested in RA, to our knowledge. In AS, Jansen et al. demonstrated a high NPV in out ruling osteoporosis using QUS [15]; however, they did not provide an explanation for their choice of T-scores of < − 1 and < − 1.5 as QUS thresholds. The ISCD do not recommend using WHO T-score criteria with peripheral devices, as they are employing different technology to assess bone health [26]; instead they recommend that device-specific cutoff points are established. Simply applying conventional DXA cutoffs in QUS measurement can underestimate the prevalence of osteoporosis [8]. Our study adds to the literature by establishing device-specific cutoffs, using an adequate sensitivity, as recommended by the ISCD.

One benefit of introducing a "triage" tool is a reduction in the demand on DXA, a resource which is heavily oversubscribed. A systematic review in postmenopausal women over the age of 45 years identified that between 3 and 63% of DXAs could be avoided by introducing QUS as a prescreen stratification tool to out rule individuals with osteoporosis [11]. In this study, using QUS to out rule a diagnosis of low BMD could have avoided up to 27% of DXAs. This has the potential to significantly ease the strain on the service. To our knowledge, this is the first study to test this in an axSpA population.

The prevalence of overt osteoporosis was low in this study. Therefore, we were unable to find any relationship between QUS and osteoporosis in participants and could not identify whether QUS has a role in discriminating participants at high risk of osteoporosis. This needs to be tested in an axSpA cohort with a higher prevalence of osteoporosis to make any determination about the usefulness of QUS in diagnosing osteoporosis.

Previous literature investigating the usefulness of QUS as an alternative to DXA used the ability to out rule osteoporosis as the discriminator [11, 28, 29]. However, in this study, we chose to investigate the ability of QUS to out rule low BMD, rather than osteoporosis. Our rationale for adopting this approach was that although the risk of fracture is highest in individuals within the osteoporotic range, most fractures in the general population occur in individuals who have a T-score within the osteopenic, rather than osteoporotic, range [30]. It is therefore important to identify people with low BMD, not only with overt

osteoporosis, to allow measures to be implemented to improve bone health [31]. Therefore, we chose to investigate if QUS could out rule low BMD.

Clowes et al. demonstrated that by identifying a device-specific threshold in a cohort of women (pre- and postmenopausal), a diagnosis of osteoporosis could be excluded at the total hip with 95% confidence [28]. The performance of QUS at the spine was not reported in the study. Although in practice an 80% level of sensitivity and specificity is often employed, we chose to follow the ISCD guidelines of a 90% sensitivity for identifying participants who have osteoporosis [26]; we did not anticipate any benefit to employ a more vigorous threshold such as that chosen by Clowes et al. [28].

We would like to acknowledge some limitations to this study. As we wished to assess the ability of QUS to detect low BMD, we limited our analysis to postmenopausal women and men over the age of 50 years, preventing extrapolation of the results to premenopausal women and younger men with axSpA. The prevalence of both osteoporosis and fragility fractures in this study was low, prohibiting any analysis of the role of QUS in either. A cost-effective analysis was not performed as part of this study, which would be required before QUS could be introduced as a prescreening tool in a wider context. The thresholds established in this study are device-specific; caution is required when extrapolating the results to other devices. It is recommended that each QUS device should be validated against DXA [8] to allow bone health classification. Finally, clinical risk factors were not taken into consideration in this study. For maximal detection of low BMD, QUS results should be interpreted in the context of the wider clinical picture.

In summary, this study demonstrates that QUS of the calcaneus could be used as a triage tool to out rule low BMD in adults with axSpA, reducing the need for onward DXA referral by up to 27%. Further research is needed to delineate the role of QUS in confidently diagnosing osteoporosis in this population. QUS is promising as a simple non-invasive tool to streamline the assessment of bone health in adults with axSpA.

Acknowledgments We would like to thank all the patients who willingly gave up their time to participate in the study. We would also like to also thank the staff of the Rheumatology Department in Tallaght University Hospital for their expertise and enthusiasm in assisting with patient recruitment. Additionally, we would like to express our deep gratitude to all the staff of the bone clinic in St. James's Hospital.

Funding information We would like to acknowledge that the corresponding author (GF) was a recipient of the Bresnihan-Molloy Scholarship from the Royal College of Physicians of Ireland, funded by AbbVie pharmaceuticals. However, AbbVie pharmaceuticals had no role in the design of the study, collection of the data, analysis, and interpretation of the data or any part of manuscript preparation.

Compliance with ethical standards

Disclosures None.

References

1. Molto A, Etcheto A, van der Heijde D, Landewe R, van den Bosch F, Bautista Molano W, Burgos-Vargas R, Cheung PP, Collantes-Estevez E, Deodhar A, El-Zorkany B, Erdes S, Gu J, Hajjaj-Hassouni N, Kiltz U, Kim TH, Kishimoto M, Luo SF, Machado PM, Maksymowych WP, Maldonado-Cocco J, Marzo-Ortega H, Montecucco CM, Ozgocmen S, van Gaalen F, Dougados M (2016) Prevalence of comorbidities and evaluation of their screening in spondyloarthritis: results of the international cross-sectional ASAS-COMOSPA study. Ann Rheum Dis 75(6):1016–1023. https://doi.org/10.1136/annrheumdis-2015-208174
2. Pray C, Feroz NI, Nigil Haroon N (2017) Bone mineral density and fracture risk in ankylosing spondylitis: a meta-analysis. Calcif Tissue Int 101(2):182–192. https://doi.org/10.1007/s00223-017-0274-3
3. Westerveld LA, Verlaan JJ, Oner FC (2009) Spinal fractures in patients with ankylosing spinal disorders: a systematic review of the literature on treatment, neurological status and complications. Eur Spine J 18(2):145–156. https://doi.org/10.1007/s00586-008-0764-0
4. Bessant R, Harris C, Keat A (2003) Audit of the diagnosis, assessment, and treatment of osteoporosis in patients with ankylosing spondylitis. J Rheumatol 30(4):779–782
5. Fitzgerald G, Gallagher P, O'Shea F (2019) Multimorbidity is common in axial spondyloarthropathy and is associated with worse disease outcomes: results from the ASRI cohort. J Rheumatol. https://doi.org/10.3899/jrheum.181415
6. Shepherd JA, Schousboe JT, Broy SB, Engelke K, Leslie WD (2015) Executive summary of the 2015 ISCD position development conference on advanced measures from DXA and QCT: fracture prediction beyond BMD. J Clin Densitom 18(3):274–286. https://doi.org/10.1016/j.jocd.2015.06.013
7. European Commission (2018) The 2018 ageing report: economic and budgetary projections for the 28 EU member states (2016-2070). Brussels. https://doi.org/10.2765/615631
8. Chin KY, Ima-Nirwana S (2013) Calcaneal quantitative ultrasound as a determinant of bone health status: what properties of bone does it reflect? Int J Med Sci 10(12):1778–1783. https://doi.org/10.7150/ijms.6765
9. Guglielmi G, de Terlizzi F (2009) Quantitative ultrasound in the assessment of osteoporosis. Eur J Radiol 71(3):425–431. https://doi.org/10.1016/j.ejrad.2008.04.060
10. Schousboe JT, Shepherd JA, Bilezikian JP, Baim S (2013) Executive summary of the 2013 international society for clinical densitometry position development conference on bone densitometry. J Clin Densitom 16(4):455–466. https://doi.org/10.1016/j.jocd.2013.08.004
11. Thomsen K, Jepsen DB, Matzen L, Hermann AP, Masud T, Ryg J (2015) Is calcaneal quantitative ultrasound useful as a prescreen stratification tool for osteoporosis? Osteoporos Int 26(5):1459–1475. https://doi.org/10.1007/s00198-014-3012-y
12. Meszaros S, Toth E, Ferencz V, Csupor E, Hosszu E, Horvath C (2007) Calcaneous quantitative ultrasound measurements predicts vertebral fractures in idiopathic male osteoporosis. Joint Bone Spine 74(1):79–84. https://doi.org/10.1016/j.jbspin.2006.04.008
13. Gonnelli S, Cepollaro C, Gennari L, Montagnani A, Caffarelli C, Merlotti D, Rossi S, Cadirni A, Nuti R (2005) Quantitative ultrasound and dual-energy X-ray absorptiometry in the prediction of fragility fracture in men. Osteoporos Int 16(8):963–968. https://doi.org/10.1007/s00198-004-1771-6
14. Speden DJ, Calin AI, Ring FJ, Bhalla AK (2002) Bone mineral density, calcaneal ultrasound, and bone turnover markers in women with ankylosing spondylitis. J Rheumatol 29(3):516–521

15. Jansen TL, Aarts MH, Zanen S, Bruyn GA (2003) Risk assessment for osteoporosis by quantitative ultrasound of the heel in ankylosing spondylitis. Clin Exp Rheumatol 21(5):599–604
16. Rudwaleit M, Landewe R, van der Heijde D, Listing J, Brandt J, Braun J, Burgos-Vargas R, Collantes-Estevez E, Davis J, Dijkmans B, Dougados M, Emery P, van der Horst-Bruinsma IE, Inman R, Khan MA, Leirisalo-Repo M, van der Linden S, Maksymowych WP, Mielants H, Olivieri I, Sturrock R, de Vlam K, Sieper J (2009) The development of assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis 68(6):770–776. https://doi.org/10.1136/ard.2009.108217
17. (1993) Consensus development conference: Diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med 94(6):646–650
18. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A (1994) Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS metrology index. J Rheumatol 21(9):1694–1698
19. GE Healthcare (2011) Achilles InSight product data sheet. http://www3.gehealthcare.com.au/~/media/documents/us-global/products/bone-health/abstracts/quantitative%20ultrasound/achilles/gehealthcare-achilles-insight-productspec.pdf. Accessed 23 Nov 2017
20. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A (1994) A new approach to defining disease status in ankylosing spondylitis: the bath ankylosing spondylitis disease activity index. J Rheumatol 21(12):2286–2291
21. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, Jenkinson T (1994) A new approach to defining functional ability in ankylosing spondylitis: the development of the bath ankylosing spondylitis functional index. J Rheumatol 21(12):2281–2285
22. Doward LC, Spoorenberg A, Cook SA, Whalley D, Helliwell PS, Kay LJ, McKenna SP, Tennant A, van der Heijde D, Chamberlain MA (2003) Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis 62(1):20–26
23. Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP (1983) Assessment of patient satisfaction in activities of daily living using a modified Stanford health assessment questionnaire. Arthritis Rheum 26(11):1346–1353
24. Creemers MC, Franssen MJ, van't Hof MA, Gribnau FW, van de Putte LB, van Riel PL (2005) Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis 64(1):127–129. https://doi.org/10.1136/ard.2004.020503
25. van der Linden S, Valkenburg HA, Cats A (1984) Evaluation of diagnostic criteria for ankylosing spondylitis. a proposal for modification of the New York criteria. Arthritis Rheum 27(4):361–368
26. Miller PD, Njeh CF, Jankowski LG, Lenchik L (2002) What are the standards by which bone mass measurement at peripheral skeletal sites should be used in the diagnosis of osteoporosis? J Clin Densitom 5(Suppl):S39–S45
27. Cryer JR, Otter SJ, Bowen CJ (2007) Use of quantitative ultrasound scans of the calcaneus to diagnose osteoporosis in patients with rheumatoid arthritis. J Am Podiatr Med Assoc 97(2):108–114
28. Clowes JA, Peel NF, Eastell R (2006) Device-specific thresholds to diagnose osteoporosis at the proximal femur: an approach to interpreting peripheral bone measurements in clinical practice. Osteoporos Int 17(9):1293–1302. https://doi.org/10.1007/s00198-006-0122-1
29. Zha XY, Hu Y, Pang XN, Chang GL, Li L (2015) Diagnostic value of osteoporosis self-assessment tool for Asians (OSTA) and quantitative bone ultrasound (QUS) in detecting high-risk populations for osteoporosis among elderly Chinese men. J Bone Miner Metab 33(2):230–238. https://doi.org/10.1007/s00774-014-0587-5
30. Compston JE, McClung MR, Leslie WD (2019) Osteoporosis. Lancet 393(10169):364–376. https://doi.org/10.1016/s0140-6736(18)32112-3
31. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R (2014) Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 25(10):2359–2381. https://doi.org/10.1007/s00198-014-2794-2

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 4 September 2019 | Revised: 15 November 2019 | Accepted: 16 November 2019

DOI: 10.1111/1756-185X.13765

ORIGINAL ARTICLE

International Journal of Rheumatic Diseases WILEY

Measuring bone density in axial spondyloarthropathy: Time to turn things on their side?

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Funding information
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Abstract

Aim: Osteoporosis in axial spondyloarthropathy (axSpA) is difficult to accurately diagnose due to osteoproliferation of the spine interfering with conventional (anteroposterior, AP) dual-energy X-ray absorptiometry (DXA). This study compares AP and lateral projections of DXA when assessing bone mineral density (BMD) of the spine and investigates the impact of osteoproliferation on AP DXA.

Method: In this cross-sectional study, structured standardized assessments collected demographic, clinical, laboratory and radiographic data. DXA assessed BMD of the spine using PA and lateral projections. Hip BMD was assessed in the usual manner. World Health Organization (WHO) criteria assessed prevalence of low BMD. Incorporating lateral DXA in the bone health assessment of axSpA was investigated. SPSS was used for statistical analysis.

Results: A total of 100 patients had paired AP and lateral DXA studies: 78% were male, mean (SD) age 52 (12) years. BMD of the spine measured by AP projection was significantly higher than BMD measured by lateral projection (mean difference 0.34 g/cm^2, 95% CI 0.30-0.37). More patients had low BMD with lateral compared to AP projection (47% vs 16%, P = .01). At the hip, 34% of patients had low BMD. Disease duration, body mass index and radiographic severity independently predicted a difference between AP and lateral measurements of the spine.

Conclusion: Lateral DXA of the spine is unaffected by osteoproliferation of the spine in axSpA and detects significantly more cases of low BMD than conventional AP DXA. Lateral DXA should be included in BMD assessment of patients with axSpA.

KEYWORDS
ankylosing spondylitis, bone mineral density, dual-energy X-ray absorptiometry, osteoporosis, spondyloarthropathy

1 | INTRODUCTION

Axial spondyloarthropathy (axSpA) is a chronic inflammatory arthritis, predominantly affecting the sacroiliac joints and spine. The Assessment in SpondyloArthritis International Society (ASAS)-COMOSPA study demonstrated a high prevalence of comorbidity in patients with axSpA,[1] noting osteoporosis as the most prevalent, affecting 13% of the surveyed population. Other investigators have similarly reported a high prevalence of low bone mineral density (BMD), although figures vary widely, ranging from 4% to greater than 50%.[2-5]

Vertebral fracture prevalence is also increased in patients with axSpA,[6-8] with mortality and potential for devastating neurological outcomes higher than the general population.[9,10] The reason for the excess vertebral fracture risk is unclear, with the relationship between osteoporosis and vertebral fractures not as clearly defined as in the general population.[11-14] The risk factors for low BMD are

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also less studied in the axSpA population,[5] and there are limited data available to recommend treatment strategies to maintain or improve BMD,[15,16] in contrast to strategies that are well delineated in the general population.[17]

Much of the difficulty with estimating BMD of the spine in axSpA is related to the inherent pathophysiology of axSpA, a process which remains incompletely understood.[18] It is thought that inflammation of the vertebrae over time can result in erosion and osteoproliferation at the attachment sites of spinal ligaments into the vertebrae, termed syndesmophytes, with complete ankylosis as its most extreme form.[19,20] Conventional dual-energy X-ray absorptiometry (DXA) of the lumbar spine assesses BMD in an anteroposterior (AP) direction.[21] In axSpA, conventional DXA is unable to distinguish between BMD of the vertebral body and osteoproliferation. BMD of the spine can thus be over-estimated when conventional DXA is used, producing an illusion of reassuringly normal BMD, when significant bone loss may have occurred.[22]

A technique where assessment of the spine is unaffected by osteoproliferation is needed to better understand the epidemiology, and ultimately consequences, of low BMD in axSpA patients. Lateral DXA scanning examines the vertebral body from the side, almost exclusively measuring trabecular bone and avoiding much of the osteoproliferation that interferes with BMD assessment of the spine when using conventional DXA.[23] Modern DXA scanners allow lateral scans of the lumbar spine to be performed in the supine position and have similar precision to AP scans.[24] Lateral DXA of the spine in axSpA has been shown in a small number of studies to detect more cases of low BMD than conventional DXA.[13,25,26] The International Society of Clinical Densitometry (ISCD) recommend that a diagnosis of osteoporosis is made if the T score of the lumbar spine, total hip or femoral neck is −2.5 or less, when compared to the reference standard of a White female aged 20-29 years from the National Health and Nutrition Examination Survey (NHANES) III database.[21] Previous studies investigating the use of lateral DXA in axSpA have been limited by lack of reference databases for lateral lumbar spine BMD, prohibiting calculation of T scores. Therefore, the utility of incorporating lateral DXA in the bone health assessment of individuals with axSpA is unknown.

The aims of this study were to:

1. Compare lateral and conventional projections of DXA in their assessment of BMD of the lumbar spine in adults with axSpA
2. Determine variables that affect the accuracy of conventional DXA
3. Assess if incorporating lateral DXA in bone health assessment affects the prevalence of low BMD.

2 | METHODS

2.1 | Study design and setting

This was an observational, cross-sectional, twin-center study. Participants were consecutively recruited between April 2017 and January 2018. The study was approved by the joint Tallaght University Hospital/St. James's Hospital Research Ethics Committee, in Dublin, Ireland. The 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) guidelines for observational studies were followed for the reporting of this study.[27]

2.2 | Population

Participants were consecutively recruited from dedicated spondylitis and general rheumatology clinics in St. James's Hospital and Tallaght University Hospital, Dublin, Ireland. Additionally, patients were identified from the axSpA database and contacted over telephone using a script to invite participation. Participants were eligible if they were adults (≥18 years of age) and fulfilled the ASAS criteria for axSpA.[28] Patients were excluded if they were pregnant, actively trying to conceive, breast-feeding, under 18 or had a history of cognitive impairment which precluded informed consent. All data collection was performed in St. James's Hospital, Dublin. Written informed consent was obtained from each participating subject.

2.3 | Demographic and disease-related data

Data collection included the following:

- demographics: gender, age, ethnicity, smoking status (never, past, current), employment status, alcohol consumption, employment status, post-menopausal status for women
- disease characteristics: symptom duration, age at diagnosis, extra-articular manifestations (uveitis, inflammatory bowel disease, psoriasis), SpA features (enthesitis, dactylitis, peripheral arthritis), physician-diagnosed history of comorbidities, axSpA treatment history (biologics, conventional synthetic disease-modifying anti-rheumatic drugs [DMARDs], non-steroidal anti-inflammatory drugs [NSAIDs])
- osteoporosis history: prior physician-diagnosed osteoporosis (yes/no), prior DXA assessment (yes/no), treatment history (calcium and vitamin D supplements, definitive osteoporosis treatment), osteoporosis risk factors (history of parental hip fracture, early menopause, history of steroid use for greater than 3 months, daily alcohol, type 1 diabetes mellitus, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism, malabsorption, chronic liver disease, eating disorder, history of transplant, hyperparathyroidism, end-stage kidney disease), fracture history (any lifetime fracture, fragility fracture)
- physical examination: tragus-to-wall, cervical rotation, modified Schober's test, lateral flexion, intermalleolar distance, chest expansion – performed according to a standardized technique[29]; height was measured to the nearest 0.1 cm, weight in kg; body mass index (BMI), expressed in kg/m^2, was defined as body weight divided by square of body height

- laboratory measurements: routine bloods (full blood count, renal profile, bone profile, liver profile, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], parathyroid hormone [PTH], vitamin D) were collected on the same day of assessment and analyzed using standard laboratory techniques. Human leucocyte antigen (HLA) B-27 antigen was reported as positive or negative. Bone turnover markers and testosterone (males only) were collected for a separate analysis.

2.4 | Outcome measures

The following validated patient-reported outcome measures were collected:

- Bath AS Disease Activity Index (BASDAI)[30]
- Bath AS Functional Index (BASFI)[31]
- AS Quality of Life (ASQoL)[32]
- Bath AS Patient Global score (BAS-G)[33]
- Health Assessment Questionnaire (HAQ).[34]

Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP and -ESR were calculated.[35] Bath AS Metrology Index (BASMI) was calculated using the measurements taken by a trained investigator during the physical assessment.[29] The modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) was calculated using lateral lumbar and cervical spine X-rays, assessing radiographic damage from a scale of 0-72.[36] Antero-posterior pelvic X-rays were performed to grade sacroiliitis according to the modified New York criteria.[37]

2.5 | BMD

BMD was assessed using a Hologic Horizon A DXA scanner. All BMD assessments were performed by one radiographer in St. James's Hospital, on the same machine. A standard protocol to obtain the measurements was strictly adhered to. Quality control and calibration were performed in accordance with international recommendations.[21] Lumbar spine BMD was measured in AP (L1-4) and lateral (L2-4) projections. BMD at the total hip and femoral neck were measured. Participants remained in the same position for AP and lateral scans: supine on the table, knees supported to adopt a flexed 90° position and arms above the head. Following analysis of the AP images, the C-arm was rotated through 90° to obtain the lateral view of the spine. Participants remained supine for the hip measurements. BMD was expressed as g/cm^2. The NHANES III data was used as reference for hip T scores. The manufacturer's database was used as the reference standard for the lumbar spine, in line with ISCD positions.[38] Separate reference databases were available for both AP and lateral lumbar spine. Z scores were not available for lateral spine DXA for male patients.

Osteoporosis was defined according to the World Health Organization (WHO) for post-menopausal women and men over the age of 50 years as normal if T score ≥−1, osteopenia if between −1 and −2.5 and osteoporosis if ≤−2.5.[39] For pre-menopausal women and men under the age of 50 years, a Z score of <−2 was considered to represent low BMD. When calculating prevalence of osteoporosis and osteopenia, only post-menopausal women and men over the age of 50 were included, in accordance with the ISCD positions.[21]

2.6 | Bias

Selection bias was minimized by using clinic and database recruitment, to ensure a representative study sample. Potential participants were phoned on two separate occasions at different times/d to minimize non-response bias. Volunteer bias was minimized by keeping the data collection time short and offering flexible appointment times.

2.7 | Statistical methods

Descriptive statistics are presented as frequencies with percentages for categorical variables, and mean with standard deviation (SD) or median with 25th and 75th percentiles as appropriate for continuous variables. Differences between AP and lateral BMD of the spine were assessed using a 2-tailed paired *T*-test. Relationships between continuous variables were assessed using Pearson's correlation coefficients (*r*) or Spearman's correlation coefficients (rho) as appropriate. Independent 2-tailed *T*-tests were used to explore differences in continuous data between two groups and analysis of variance (ANOVA) for three or more groups. Mann-Whitney *U* (two groups) or Kruskall-Wallis (three or more groups) tests were used to compare continuous non-parametric variables. Chi-square tests were used to compare categorical variables.

The difference between AP and lateral BMD was calculated using the formula "AP minus lateral BMD" and expressed as a new variable in g/cm^2. We developed a model to investigate the association between independent variables and the difference between AP and lateral BMD (dependent variable). Univariable analysis was performed to identify variables associated with the dependent variable and tested in simple linear regression. All variables with a *P* value of <.1 in crude analysis were entered into the regression model, along with clinically relevant variables. Normality of residuals and multicollinearity were assessed. IBM SPSS version 24 was used for statistical analysis. A *P* value of <.05 was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

A total of 110 individuals were recruited between May 2017 and January 2018 (see Figure 1 for flow chart). Ten participants were unable to have DXA imaging of the spine, thus 100 participants with paired AP and lateral DXA of the lumbar spine were included.

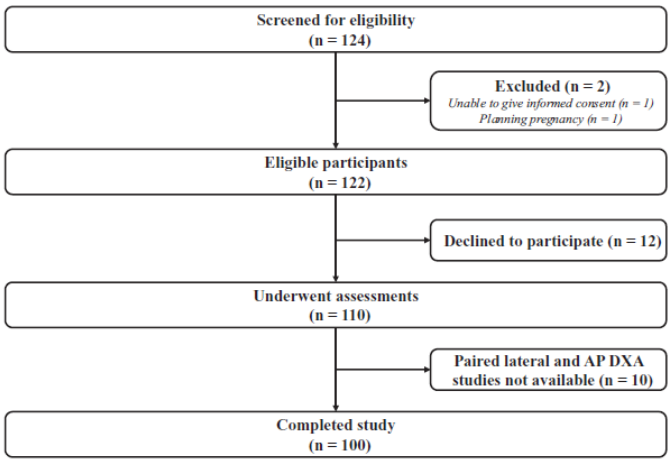

FIGURE 1 Summary of recruitment process of participants. AP, anteroposterior; DXA, dual-energy X-ray absorptiometry

Participant baseline characteristics are outlined in Table 1. Briefly, 78% (n = 78) were male, 98% (n = 98) Caucasian, mean (SD) age was 51.6 (11.6) years and median (25th, 75th) disease duration was 23.6 (14.4, 34.9) years, with a median delay to diagnosis of 7 (2, 13.5) years. The median (25th, 75th) mSASSS was 10 (interquartile range 4-37.3). Eight percent (n = 8) of participants had no osteoproliferation on imaging (mSASSS = 0) and 8% (n = 8) had a "bamboo spine" (mSASSS = 72).

Forty percent (n = 40) of the cohort had previously had a DXA assessment of their BMD. Seven percent (n = 7) of participants reported a prior diagnosis of osteoporosis. Although 44% (n = 44) of participants reported a history of any fracture in their lifetime, fragility fracture prevalence was low in the cohort (3%, n = 3). One-third of the cohort (n = 33, 33%) had at least 1 risk factor for osteoporosis: exposure to steroids for greater than 3 months was the most common risk factor (n = 14), followed by a history of parental hip fracture (n = 8). Five patients had a history of current or past definitive osteoporosis treatment.

3.2 | Measured BMD of spine (AP and lateral projections of DXA) and hip

Mean BMD of spine and hip are outlined in Table 1. All measured sites of BMD correlated positively with each other. BMD of the spine measured by AP (conventional) projection correlated positively with age, mSASSS and BASMI, indicating that AP BMD of the spine increased in older patients and patients with higher mSASSS and BASMI scores (Table 2). In contrast, BMD of the spine measured by lateral projection showed no correlation with mSASSS or BASMI, and a non-significant inverse correlation with age; similar patterns were found at the hip. Men had higher BMD than women at the spine (both projections) and the hip; smoking status, exposure to biologic treatment, HLA-B27 positivity or presence of osteoporosis risk factors had no impact on BMD (Table S1).

3.3 | Comparison of lumbar spine BMD using AP and lateral DXA

BMD of the lumbar spine measured by AP projection was significantly higher than when BMD is measured by lateral projection (mean difference 0.34 g/cm^2, 95% CI 0.30-0.37), as demonstrated in Figure 2. The difference between AP and lateral measurements of lumbar spine BMD (AP minus lateral BMD) correlated with age, mSASSS, BASMI, BMI and BASFI (see Table 2). This indicated that the older the patient or the more severe the disease, the bigger the difference between the AP (conventional) and the lateral BMD measurement. The difference between AP and lateral BMD of the spine was similar in men and women (mean difference between genders was 0.04 g/cm^2, 95% CI −0.04 to 0.12). Additionally, there was no correlation between AP and lateral BMD difference and inflammatory markers or vitamin D ($P > .05$).

3.4 | Assessment of variables associated with difference between AP and lateral BMD

We developed a model to investigate variables associated with the difference between AP and lateral BMD, as outlined in the methods section. We additionally controlled for gender and exposure to treatment with biologics, as clinically relevant variables. After correcting for multicollinearity, the R^2 of the final model was 0.4 (Table 3). Disease duration, BMI and mSASSS remained independently associated with the difference between AP and lateral BMD of the spine.

TABLE 1 Baseline demographic and clinical characteristics of the axSpA cohort

Variable	Whole population (N = 100)
Males; n (%)	78 (78)
Age, y, mean (SD)	51.6 (11.6)
Caucasian; n (%)	98 (98)
Disease duration, y, mean (SD)	25.7 (12.9)
Delay to diagnosis, y, mean (SD)	8.9 (8.6)
Employment status; n (%)	
Employed	54 (54)
Disability due to axSpA	15 (15)
Smoking status; n (%)	
Current	25 (25)
Past	47 (47)
Never	28 (28)
Post-menopausal women,[a] n (%)	13 (59)
HLA-B27 positive,[b] n (%)	83 (84.7)
BMI, kg/m^2, mean (SD)	28.1 (5.5)
Modified New York criteria, n (%)	85 (85)
Extra-articular manifestations, n (%)	
Uveitis	29 (29)
Psoriasis	16 (16)
IBD	16 (16)
Treatment; n (%)	
NSAIDs	43 (43)
Steroids use > 3 mo	14 (14)
Biologic exposure	70 (70)
Calcium supplement	17 (17)
Vitamin D supplement	26 (26)
Disease severity; median (25th, 75th percentile)	
ASDAS-CRP	2.2 (1.6, 3.0)
ASDAS-ESR	2.0 (1.3, 2.9)
BASDAI	3.9 (2.1, 5.6)
BASFI	4.0 (1.4, 5.7)
BASMI	4.2 (2.8, 6)
HAQ	0.63 (0.13, 1.00)
ASQoL	6 (2, 11)
mSASSS	10 (4, 37.3)
Self-reported fragility fracture, n (%)	3 (3)
Osteoporosis risk factor, any, n (%)	33 (33)
Bone mineral density, g/cm^2, mean (SD)	
PA lumbar spine	1.08 (0.19)
Lateral lumbar spine	0.74 (0.14)
Femoral neck	0.80 (0.11)
Total hip	0.96 (0.12)

Abbreviations: ASQoL, Ankylosing Spondylitis Quality of Life; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath AS Disease Activity Index; BASFI, Bath AS Functional Index; BASMI, Bath AS Metrology Index; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; HLA, human leucocyte antigen; IBD, inflammatory bowel disease; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; NSAIDS, non-steroidal anti-inflammatory drugs; PA, postero-anterior; PTH, parathyroid hormone.

[a]Calculated as % of women (n = 22) in study.

[b]HLA-B27 status unknown in n = 2.

3.5 | Prevalence of low BMD

Fifty-seven patients fulfilled criteria for classification of BMD using T scores (ie men ≥ 50 years and post-menopausal women). Of this cohort, 16% had low BMD of the spine when measured by AP DXA, compared to 47% when measured by lateral DXA (Chi-square 7.4, P = .01, odds ratio 12.2, 95% CI 1.4-106), as outlined in Figure 3. At the hip, 34% (n = 19) had low BMD at either femoral neck or total hip.

As per the WHO definition,[37] hip and spine data were combined to assess for low BMD at any site. When AP spine BMD was combined with hip BMD, 35% (n = 20) of patients had low BMD at a minimum of one site. However, when lateral spine BMD was combined with hip BMD, 56% (n = 32) of patients had low BMD, a statistically significant difference (Chi-square 18.9, degree of freedom 1, P < .001).

Including both AP and lateral spine in combination with hip data, 58% (n = 33) of the cohort had low BMD and 18% (n = 10) had osteoporosis at a minimum of one site.

Z scores for lateral lumbar spine BMD are not available in men, therefore similar data cannot be presented for the remainder of the population.

4 | DISCUSSION

Osteoporosis is widely accepted to occur at an increased prevalence in axSpA compared to age- and sex-matched controls. However, accurately assessing BMD of the spine is challenging in axSpA patients due to the overestimation that occurs from calcification and osteoproliferation.[40] Therefore, the primary aim of this study was to compare AP and lateral DXA in their ability to measure BMD of the spine and assess the impact of osteoproliferation.

In this study of 100 axSpA patients, we demonstrated that when directly compared, raw BMD of the spine expressed in g/cm^2 was significantly lower when measured by lateral projection of DXA than by conventional AP DXA, confirming findings by other researchers.[25,41] We then explored the association of a number of participants and disease-related variables with AP and lateral DXA, in an attempt to explain the difference between the two methods. We demonstrated that AP BMD of the spine increased with age, in contrast to the expected decline in BMD that occurs with age in the general population. AP BMD also increased as mSASSS and BASMI increased, both indicators of structural severity. These associations were not seen when BMD of the spine was measured by lateral DXA, or with hip BMD. Therefore, longer disease duration and more severe disease affected AP DXA assessment of the spine, but not lateral DXA.

We also demonstrated that the difference in BMD between AP and lateral DXA increased with longer disease duration and higher mSASSS. After controlling for BMI due to its effect on measurement of BMD from soft tissue interference,[42,43] mSASSS and disease duration remained independent predictors of the difference between AP and lateral DXA of the spine. This important finding signifies that structural damage in the form of osteoproliferation is interfering with the accuracy of what is currently our "gold standard" technique to assess BMD

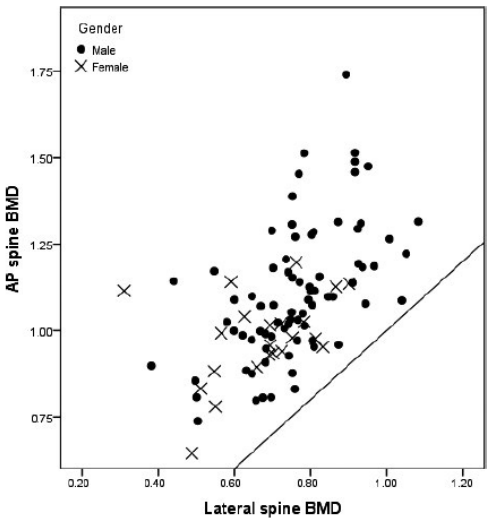

FIGURE 2 Scatter plot demonstrating difference between BMD of the spine as measured by AP and lateral DXA, stratified by gender. Dashed line represents reference for no difference between AP and lateral BMD. AP, anteroposterior; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry

in axSpA patients.[21] Therefore, continuing to rely solely on AP DXA to evaluate BMD of the spine in axSpA is no longer acceptable.

The clinical significance of BMD is not in the raw BMD expressed in g/cm^2, but in its WHO classification as normal or low BMD using T scores, as it is this which is clearly associated with morbidity and mortality in the general population.[44,45] Previously, the ability of lateral spine DXA to detect low BMD in axSpA was limited by lack of adequate reference databases in other studies to compute T scores for lateral lumbar spine.[25,26] In our study, a manufacturer-compiled reference database for lateral lumbar spine BMD allowed us to compute specific T scores (but unfortunately not *Z* scores) for both men and women for lateral lumbar spine, to our knowledge the first study to do so in axSpA. Therefore, we compared the ability of lateral and AP DXA to measure BMD and found that lateral DXA detected significantly more cases of low BMD (47%) than did AP DXA (16%).

In practice, a diagnosis of low BMD is made if a patient fulfills WHO criteria for either osteopenia or osteoporosis of at least 1 site of spine or hip.[39,46] In this study, using lateral DXA in place of AP DXA improved our diagnosis of low BMD significantly from 35% to 56%. Using both AP and lateral spine DXA results, along with hip data, increased the diagnosis of low BMD to 58%. Had we relied on hip data alone, as advocated by some clinicians,[26] only 34% of patients would have received a diagnosis of low BMD. Thus, using lateral DXA in addition to AP DXA to assess BMD improves our ability to detect low BMD in axSpA. In the general population, lateral DXA has been shown to identify more cases of low BMD than conventional DXA.[23,47] However, to our knowledge, this is the first study in axSpA to show this.

It has been the subject of much debate as to whether osteoporosis in axSpA is localized to the spine or is a more systemic process.[41,48-50] We demonstrated a higher prevalence of low BMD at the spine compared to the hip, suggesting the spine is affected to a more significant degree than are the hips. Therefore, it is important that we have a method to accurately assess BMD of the spine, which is not affected by the severity of disease. We note the interesting results of a recent study published[26] which was the first to examine lateral measurements

TABLE 2 Correlation between variables and (a) each measured BMD site (b) difference between AP and lateral BMD

(a)	Lateral spine BMD[a]	FN BMD[a]	TH BMD[a]	Age[a]	BMI[a]	mSASSS[b]	BASMI[a]
AP spine BMD	0.55**	0.48**	0.52**	0.23*	0.43**	0.41**	0.48**
Lateral spine BMD	…	0.43**	0.55**	-0.12	0.21*	0.07	0.02
FN BMD	…	…	0.82**	-0.19	0.18	0.00	0.02
TH BMD	…	…	…	-0.15	0.34**	-0.03	-0.06
Age	…	…	…	…	0.13	0.55**	0.58
BMI	…	…	…	…	…	0.28**	0.30**
mSASSS	…	…	…	…	…	…	0.77**
(b)	**Age[a]**	**BASDAI[a]**	**BASMI[a]**	**mSASSS[b]**	**BASFI[a]**	**CRP[a]**	**BMI[a]**
AP – lateral BMD	0.38**	0.01	0.54**	0.51**	0.32**	0.03	0.32**

Note: … denotes duplicate cell, left blank for clarity of presentation.

Abbreviations: AP, anteroposterior; BASDAI, Bath AS disease activity index; BASFI, Bath AS functional index; BASMI, Bath AS metrology index; BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FN, femoral neck; mSASSS, modified Stokes Ankylosing Spondylitis Score; TH, total hip.

[a]Correlation coefficient is Pearson's *r*.

[b]Correlation coefficient is Spearman correlation coefficient, rho.

*$P < .05$.

**$P < .01$.

TABLE 3 Multiple regression model, variables associated with difference between AP and lateral BMD of the spine

Variable	β	95% CI	P value
Gender[a]	−0.028	−0.093 to 0.037	.40
Disease duration	0.003	0.001 to 0.005	.01
Biologic exposure[b]	0.015	−0.043 to 0.072	.60
BMI	0.009	0.003 to 0.014	<.01
mSASSS	0.002	0.001 to 0.004	<.01

Abbreviations: AP, anteroposterior; BMI, body mass index; CI, confidence interval; mSASSS, modified Stokes Ankylosing Spondylitis Spinal Score.

[a]Reference group (0) is male.

[b]Reference group (0) is no biologic exposure.

of the spine longitudinally and unexpectedly found that both lateral and AP BMD increased over time. However, there were no reference values available for lateral BMD measurements in the men, so the authors urge caution with interpretation of this finding.

We would like to acknowledge some limitations. This is a cross-sectional study, which prohibits comment on causality – we can merely comment on associations. The population is almost exclusively Caucasian, thus caution must be applied when extrapolating results to other ethnicities. Reference values to calculate *Z* scores for lateral spine BMD were unavailable, thus we cannot comment on prevalence of low BMD in men under 50 years and pre-menopausal women. As this sub-group represented a large portion of our cohort, the strength of our results would have increased had this been available, therefore this represents a limitation. However, the differences between raw BMD values are valid in the entire population. Finally, the clinical significance of osteoporosis is in its associated fracture risk; however, the prevalence of fragility fractures was low in this study. This prevented any definitive conclusions regarding the association between BMD and vertebral fractures. The clinical outcomes of vertebral fractures in patients with axSpA are worse than other populations,[9] so it is crucial to understand the role BMD plays in this increased susceptibility. Therefore, future research needs to determine whether there is a correlation between BMD as measured by lateral DXA and vertebral fracture risk.

This study has many strengths. The patients are well-characterized, with an extensive data set collected. It is a homogenous population, allowing easy extrapolation of the results. All efforts were made to limit sources of bias, thus ensuring our population is representative of the axSpA population.

In summary, BMD of the lumbar was significantly lower when measured by lateral DXA than AP DXA. The difference between lateral and AP DXA increased with higher mSASSS. Including lateral DXA in the bone health assessment significantly increased the prevalence of low BMD in this population. Lateral DXA should be routinely added to the BMD assessment of individuals with axSpA.

ACKNOWLEDGEMENTS

We thank all the patients who so willingly participated in the study. We would like to also thank Professors David Kane and Ronan Mullan of Tallaght University Hospital for their enthusiastic contribution in providing patients for this study. Additionally, we would like to express our deep gratitude to all the nursing and administrative staff of the Bone Clinic in St. James's Hospital; without their extensive assistance and guidance, this project would never have succeeded.

AUTHORS CONTRIBUTIONS

GF was involved in the conception and design of the study, acquisition of data, statistical analysis, interpretation of data and drafting of the manuscript. KMcC and FOS were involved in the conception and design of the study, statistical analysis, interpretation of data and critically revising the manuscript. TA participated in design of the study and data acquisition, statistical analysis and drafting of the manuscript. All authors read and approved the final version of the manuscript.

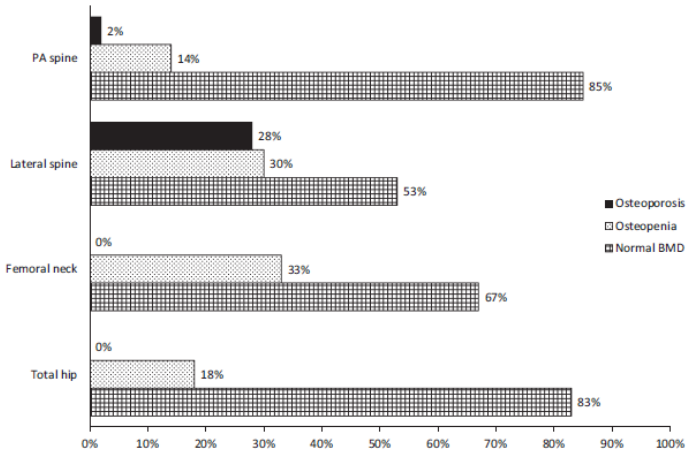

FIGURE 3 Prevalence of normal BMD, osteopenia and osteoporosis at each measured site, in men ≥ 50 years and post-menopausal women (n = 57). AP, anteroposterior; BMD, bone mineral density

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REFERENCES

1. Moltó A, Etcheto A, van der Heijde D, et al. Prevalence of comorbidities and evaluation of their screening in spondyloarthritis: results of the international cross-sectional ASAS-COMOSPA study. *Ann Rheum Dis*. 2016;75(6):1016-1023.
2. Akgol G, Kamanli A, Ozgocmen S. Evidence for inflammation-induced bone loss in non-radiographic axial spondyloarthritis. *Rheumatology (Oxford)*. 2014;53(3):497-501.
3. Nigil Haroon N, Szabo E, Raboud JM, et al. Alterations of bone mineral density, bone microarchitecture and strength in patients with ankylosing spondylitis: a cross-sectional study using high-resolution peripheral quantitative computerized tomography and finite element analysis. *Arthritis Res Ther*. 2015;17:377.
4. Forien M, Molto A, Etcheto A, Dougados M, Roux C, Briot K. Bone mineral density in patients with symptoms suggestive of spondyloarthritis. *Osteoporos Int*. 2015;26(5):1647-1653.
5. Ramirez J, Nieto-Gonzalez JC, Curbelo Rodriguez R, Castaneda S, Carmona L. Prevalence and risk factors for osteoporosis and fractures in axial spondyloarthritis: a systematic review and meta-analysis. *Semin Arthritis Rheum*. 2018;48(1):44-52.
6. Vosse D, Landewé R, van der Heijde D, van der Linden S, van Staa T-P, Geusens P. Ankylosing spondylitis and the risk of fracture: results from a large primary care-based nested case-control study. *Ann Rheum Dis*. 2009;68(12):1839-1842.
7. Robinson Y, Sanden B, Olerud C. Increased occurrence of spinal fractures related to ankylosing spondylitis: a prospective 22-year cohort study in 17,764 patients from a national registry in Sweden. *Patient Saf Surg*. 2013;7(1):2.
8. Montala N, Juanola X, Collantes E, et al. Prevalence of vertebral fractures by semiautomated morphometry in patients with ankylosing spondylitis. *J Rheumatol*. 2011;38(5):893-897.
9. Westerveld LA, Verlaan JJ, Oner FC. Spinal fractures in patients with ankylosing spinal disorders: a systematic review of the literature on treatment, neurological status and complications. *Eur Spine J*. 2009;18(2):145-156.
10. Westerveld LA, van Bemmel JC, Dhert WJ, Oner FC, Verlaan JJ. Clinical outcome after traumatic spinal fractures in patients with ankylosing spinal disorders compared with control patients. *Spine J*. 2014;14(5):729-740.
11. Geusens P, De Winter L, Quaden D, et al. The prevalence of vertebral fractures in spondyloarthritis: relation to disease characteristics, bone mineral density, syndesmophytes and history of back pain and trauma. *Arthritis Res Ther*. 2015;17(1):294.
12. Klingberg E, Geijer M, Göthlin J, et al. Vertebral fractures in ankylosing spondylitis are associated with lower bone mineral density in both central and peripheral skeleton. *J Rheumatol*. 2012;39(10):1987-1995.
13. Ulu MA, Cevik R, Dilek B. Comparison of PA spine, lateral spine, and femoral BMD measurements to determine bone loss in ankylosing spondylitis. *Rheumatol Int*. 2013;33(7):1705-1711.
14. Donnelly S, Doyle DV, Denton A, Rolfe I, McCloskey EV, Spector TD. Bone mineral density and vertebral compression fracture rates in ankylosing spondylitis. *Ann Rheum Dis*. 1994;53(2):117-121.
15. Braun J, van den Berg R, Baraliakos X, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis*. 2011;70(6):896-904.
16. van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis*. 2017;76(6):978-991.
17. Black DM, Rosen CJ. Clinical Practice. Postmenopausal osteoporosis. *N Engl J Med*. 2016;374(3):254-262.
18. Haroon N. Ankylosis in ankylosing spondylitis: current concepts. *Clin Rheumatol*. 2015;34(6):1003-1007.
19. Magrey MN, Khan MA. The paradox of bone formation and bone loss in ankylosing spondylitis: evolving new concepts of bone formation and future trends in management. *Curr Rheumatol Rep*. 2017;19(4):17.
20. Van Mechelen M, Gulino GR, de Vlam K, Lories R. Bone disease in axial spondyloarthritis. *Calcif Tissue Int*. 2018;102(5):547-558.
21. Schousboe JT, Shepherd JA, Bilezikian JP, Baim S. Executive summary of the 2013 international society for clinical densitometry position development conference on bone densitometry. *J Clin Densit*. 2013;16(4):455-466.
22. Carter S, Lories RJ. Osteoporosis: a paradox in ankylosing spondylitis. *Curr Osteoporos Rep*. 2011;9(3):112-115.
23. Finkelstein JS, Cleary RL, Butler JP, et al. A comparison of lateral versus anterior-posterior spine dual energy x-ray absorptiometry for the diagnosis of osteopenia. *J Clin Endocrinol Metabol*. 1994;78(3):724-730.
24. Blake GM, Jagathesan T, Herd RJ, Fogelman I. Dual X-ray absorptiometry of the lumbar spine: the precision of paired anteroposterior/lateral studies. *Br J Radiol*. 1994;67(799):624-630.
25. Malochet-Guinamand S, Pereira B, Tatar Z, et al. Prevalence and risk factors of low bone mineral density in spondyloarthritis and prevalence of vertebral fractures. *BMC Musculoskelet Disord*. 2017;18(1):357.
26. Deminger A, Klingberg E, Lorentzon M, et al. Which measuring site in ankylosing spondylitis is best to detect bone loss and what predicts the decline: results from a 5-year prospective study. *Arthritis Res Ther*. 2017;19(1):273.
27. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med*. 2007;147(8):573-577.
28. Rudwaleit M, Landewe R, van der Heijde D, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis*. 2009;68(6):770-776.
29. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. *J Rheumatol*. 1994;21(9):1694-1698.
30. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol*. 1994;21(12):2286-2291.
31. Calin A, Garrett S, Whitelock H, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol*. 1994;21(12):2281-2285.
32. Doward LC, Spoorenberg A, Cook SA, et al. Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. *Ann Rheum Dis*. 2003;62(1):20-26.
33. Jones SD, Steiner A, Garrett SL, Calin A. The Bath Ankylosing Spondylitis Patient Global Score (BAS-G). *Br J Rheumatol*. 1996;35(1):66-71.
34. Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum*. 1983;26(11):1346-1353.
35. Lukas C, Landewé R, Sieper J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis*. 2009;68(1):18-24.
36. Creemers MC, Franssen MJ, van't Hof MA, Gribnau FW, van de Putte LB, van Riel PL. Assessment of outcome in ankylosing

spondylitis: an extended radiographic scoring system. *Ann Rheum Dis*. 2005;64(1):127-129.
37. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum*. 1984;27(4):361-368.
38. Shepherd JA, Schousboe JT, Broy SB, Engelke K, Leslie WD. Executive summary of the 2015 ISCD Position Development Conference on Advanced Measures From DXA and QCT: fracture prediction beyond BMD. *J Clin Densit*. 2015;18(3):274-286.
39. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med*. 1993;94(6):646-650.
40. Fitzgerald GE, O'Shea FD. The fascinating paradox of osteoporosis in axial spondyloarthropathy. *J Rheumatol*. 2017;44(12):1767-1776.
41. Klingberg E, Lorentzon M, Mellstrom D, et al. Osteoporosis in ankylosing spondylitis - prevalence, risk factors and methods of assessment. *Arthritis Res Ther*. 2012;14(3):R108.
42. Rajamanohara R, Robinson J, Rymer J, Patel R, Fogelman I, Blake GM. The effect of weight and weight change on the long-term precision of spine and hip DXA measurements. *Osteoporos Int*. 2011;22(5):1503-1512.
43. Patel R, Blake GM, Rymer J, Fogelman I. Long-term precision of DXA scanning assessed over seven years in forty postmenopausal women. *Osteoporos Int*. 2000;11(1):68-75.
44. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. *Lancet*. 2002;359(9321):1929-1936.
45. Qu X, Huang X, Jin F, et al. Bone mineral density and all-cause, cardiovascular and stroke mortality: a meta-analysis of prospective cohort studies. *Int J Cardiol*. 2013;166(2):385-393.
46. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. *World Health Organ Tech Rep Ser*. 1994;843:1-129.
47. Zmuda JM, Cauley JA, Glynn NW, Finkelstein JS. Posterior-anterior and lateral dual-energy x-ray absorptiometry for the assessment of vertebral osteoporosis and bone loss among older men. *J Bone Miner Res*. 2000;15(7):1417-1424.
48. Karberg K, Zochling J, Sieper J, Felsenberg D, Braun J. Bone loss is detected more frequently in patients with ankylosing spondylitis with syndesmophytes. *J Rheumatol*. 2005;32(7):1290-1298.
49. Toussirot E, Michel F, Wendling D. Bone density, ultrasound measurements and body composition in early ankylosing spondylitis. *Rheumatology (Oxford)*. 2001;40(8):882-888.
50. Sarikaya S, Basaran A, Tekin Y, Ozdolap S, Ortancil O. Is osteoporosis generalized or localized to central skeleton in ankylosing spondylitis? *J Clin Rheumatol*. 2007;13(1):20-24.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Fitzgerald G, Anachebe T, McCarroll K, O'Shea F. Measuring bone density in axial spondyloarthropathy: Time to turn things on their side?. *Int J Rheum Dis*. 2020;00:1–9. https://doi.org/10.1111/1756-185X.13765

The Journal of Rheumatology

The Journal of Rheumatology Volume 44, no. 12

The Fascinating Paradox of Osteoporosis in Axial Spondyloarthropathy

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J Rheumatol 2017;44;1767-1776
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Review

The Fascinating Paradox of Osteoporosis in Axial Spondyloarthropathy

Gillian E. Fitzgerald and Finbar D. O'Shea

ABSTRACT. Low bone mineral density (BMD) is a recognized feature of axial spondyloarthropathy (axSpA). However, the osteoproliferation inherent in axSpA can make traditional dual-energy x-ray absorptiometry assessment inaccurate, particularly in structurally advanced disease. As a result, much about osteoporosis in axSpA is unknown. There is a wide variation in prevalence figures for low BMD in the literature. There is also no consensus regarding risk factors for developing low BMD in axSpA. It is accepted that there is an excess of vertebral fractures in patients with axSpA, but the role of low BMD in contributing to this risk is virtually unknown. This article provides a comprehensive review of the current knowledge regarding low BMD in axSpA. It highlights our current BMD measurement techniques along with their potential pitfalls, and discusses the significance of BMD in vertebral fractures. It also identifies gaps in our knowledge and makes recommendations for future research. (First Release October 1 2017; J Rheumatol 2017;44:1767–76; doi:10.3899/jrheum.170051)

Key Indexing Terms:
AXIAL SPONDYLOARTHROPATHY
BONE MINERAL DENSITY
OSTEOPOROSIS
DUAL-ENERGY X-RAY ABSORPTIOMETRY

Osteoporosis can be defined as "a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture"[1]. It is a recognized entity in many inflammatory diseases. In rheumatoid arthritis, it is widely accepted that low bone mineral density (BMD) is an extraarticular feature of the disease[2], with the prevalence of osteoporosis up to twice that of the general population and an increased risk of fractures. Similar data have been shown in juvenile idiopathic arthritis, where generalized loss of BMD and an excess of fractures, both vertebral and nonvertebral, are noted[3]. In psoriatic arthritis, the data are less robust, but point toward a high prevalence of low BMD[4].

BMD in Axial Spondyloarthropathy

There is growing interest in BMD in axial spondyloarthropathy (axSpA). It is now accepted that patients with axSpA have a higher prevalence of both osteopenia and osteoporosis, when compared to age- and sex-matched controls. However, the reported prevalence of low BMD varies widely, ranging from 4% to 58% (Table 1)[5–30]. There are many reasons underlying this discrepancy. First, there is a wide variation in the patient recruitment techniques used. Second, different techniques are used to evaluate BMD. A further confounder is the change in classification criteria published by the Assessment of Spondyloarthritis International Society in 2009[31]. Older studies exclusively used patients with ankylosing spondylitis (AS) as defined by the modified New York criteria, whereas newer ones use a combination of patients with axSpA and patients with AS. All these factors make it difficult to compare the existing literature accurately, thus limiting our understanding of the scale of the problem.

There are many undisputed facts. Almost all the literature agrees that patients with established axSpA have a higher prevalence of low BMD than controls (Table 1). However, this problem is not restricted to late disease. BMD begins to decline early in the disease process, with low BMD evident in 40–50% of axSpA patients with an average disease duration of only 6 years[29]. A diagnosis of axSpA is associated with low BMD, regardless of disease duration. In fact, the presence of low BMD, defined as a T score of ≤ –2 SD, has been shown to have good predictive value (positive likelihood ratio of 2.6–3.1) in diagnosing axSpA in patients with suggestive symptoms[12]. Another study also found that patients with nonradiographic (nr)-axSpA had significantly lower lumbar spine BMD than patients with mechanical lower back pain[5].

Measurement Techniques to Detect Low BMD

Currently, the gold standard for assessing BMD is posteroan-

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Accepted for publication July 11, 2017.

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Table 1. Summary of studies outlining prevalence of low BMD in axial spondyloarthritis.

Author	Design	Recruitment	Study Population	N (M/F)	Disease Duration, yrs, mean	BMD Measurement Technique(s)	Result
Akgol[5]	Cross-sectional	Consecutive	LBP[§]	46 (32/14)	1.25	DEXA: AP LS, FN	LS BMD lower in nr-axSpA than mLBP patients. Low BMD associated with spinal inflammation on MRI (LS, FN).
Arends[6]	Cross-sectional	Consecutive	AS[†]	128 (93/35)	14	DEXA: AP LS, PF	57% had LS or TF BMD T score ≤ –1. Difference between LS and TF BMD positively correlated with disease duration.
Briot[7]	Cross-sectional	DESIR* cohort baseline visit	IBP[††] axSpA criteria: 71.4%	332 (174/158)	M: 1.6, F: 1.7	DEXA: LS, TF, FN	Low BMD: 11.5% LS, 4.2% hip, 13% both sites. LS BMD significantly lower in patients with BME. Lower BMD (LS, TF) in patients fulfilling ASAS criteria.
Capaci[8]	Cross-sectional	NR	AS[†]	73 (49/24)	11.8	DEXA: AP LS, TF	Mild AS: low BMD 68.4% at LS, 51.9% TF. Advanced AS: low BMD 54.3% at LS, 91.7% TF. LS BMD similar in mild and advanced AS. Frequency of osteoporosis (TF) higher in patients with advanced AS.
Devogelaer[9]	Cross-sectional	NR	AS[†]	70 (60/10)	15.4	SPA: radius DEXA: LS SE-QCT: LS	DEXA LS BMD significantly lower in patients than controls. QCT: BMD lower in patients than controls.
Donnelly[10]	Cross-sectional	Consecutive	AS[#]	87 (62/25)	M: 16.3, F: 16.6	DEXA: AP LS, FN, WB	LS BMD significantly lower in M than F. BMD reduced in LS and FN in early disease. LS BMD increased in late disease. FN BMD further decreased in late disease.
El Maghraoui[11]	Cross-sectional	Consecutive	AS[†]	43 (43/0)	6.8	QCT: LS	Mean LS BMD significantly lower in patients with AS than controls.
Forien[12]	Cross-sectional	Retrospective	axSpA[†††]	193 (122/71)	11.2	DEXA: AP LS, FN, TF	Prevalence of low BMD: 26.4% (LS), 13.6% (TF), 40.3% (at least 1 site).
			axSpA, n = 193				Nr-axSpA: LS BMD lower than controls (T score ≤ –2 in 28.1% vs 9.7%; p = 0.01).
			nr-axSpA, n = 61				LR+ of low BMD for axSpA diagnosis: 2.6 (LS), 3.12 (TF).
							LR+ of low BMD for nr-axSpA diagnosis: 2.9 (LS), 2.54 (TF).
Geusens[13]	Cross-sectional	Consecutive	SpA[‡‡]	390 (175/215)	10.8	DEXA: AP LS, FN, TF	T score ≥ –1: 79.7% (LS), 59.5% (FN).
			73.3% AS, 10.3% PsA, 4.6% EnA, 11.8% uSpA				T score between –1 and –2.5: 17.2% (LS), 36.4% FN.
							T score ≤ –2.5: 3.1% (LS), 4.1% (FN).
Ghozlani[14]	Cross-sectional	Consecutive	AS[†]	80 (67/13)	10.8	DEXA: AP LS, FN, TF	Prevalence of osteoporosis at any site: 25%
Gratacos[15]	Longitudinal	Consecutive	AS[‡‡]	34 (27/7)	Active AS: 7.5	DEXA: AP LS, FN	Active AS had significant bone mass loss at LS (5%) and FN (3%).
	Mean followup 19 mos				Inactive AS: 5.3		
Grazio[16]	Cross-sectional	Random	AS[†]	80 (46/34)	21.8	DEXA: AP LS, TF, FN	Osteopenic: 20% LS, 26.2% TF, 47.5% FN. Osteoporotic: 25% LS, 7.5% TF, 22.5% FN. Significantly more patients osteoporotic at LS than TF.
Nigil Haroon[17]	Cross-sectional	Toronto Western Hospital Spondylitis Clinic	AS[†]	53 (29/24)	17	DEXA: AP LS, FN, TF HRpQCT: distal radius and tibia	Osteopenia: 34% (M: 31%, F: 38%). Osteoporosis: 11% (M: 10%, F: 13%). vBMD lower at distal radius and tibia in AS than controls.

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Table 1. Continued.

Author	Design	Recruitment	Study Population	N (M/F)	Disease Duration, yrs, mean	BMD Measurement Technique(s)	Result
Jun[18]	Cross-sectional	Consecutive	AS†	68 (68/0)	68 mo	DEXA: PA LS, TF, FN	Lower BMD in AS patients (LS, TF, FN) than controls.
Karberg[19]	Cross-sectional	Consecutive	AS†	103 (66/37)	I (≤ 5 yrs): 2.5 II (5–10 yrs): 7 III (> 10 yrs): 19.7	DEXA: AP LS, FN DEQCT: LS pQCT: radius	Prevalence (%) of osteopenia and osteoporosis at each site: DEXA LS: 31, 14 DEQCT LS: 44, 11 DEXA FN: 52, 24 pQCT radius: 16, 1. DEXA FN classified more osteoporosis than DEXA LS or DEQCT in longer disease. DEQCT classified increasing % of patients as osteoporosis with increasing disease duration; DEXA LS was the opposite.
Klingberg[20]	Cross-sectional	Randomized from larger osteoporosis study[21]	AS†	69 (69/0)	23	DEXA: AP LS, lat LS, FN, TF, radius QCT: LS HRpQCT: radius and tibia	vBMD lower in AS than controls by HRpQCT (radius/tibia). Prevalence (%) of osteopenia and osteoporosis at LS: AP DEXA: 19, 6 QCT: 30, 38
Klingberg[21]	Cross-sectional	Invited from database	AS†	204 (117/87)	24	DEXA: AP LS, lat LS, FN, TF, radius	≥ 50 yrs: osteopenia 43.6%, osteoporosis 20.8%. < 50 yrs: 4.9% low BMD. LS most common location for low BMD, followed by radius, then FN. Lat LS significantly lower than AP LS BMD.
Korkosz[22]	Longitudinal 10-yr followup	NR	AS†	15 (15/0)	16.5	DEXA: AP LS, TF, FN SE-QCT: LS	QCT baseline: n = 5 osteopenia, n = 6 osteoporosis. Significant decrease in BMD in LS by QCT over 10 yrs. DEXA LS: increased BMD. FN/TF: no significant change in BMD. No correlation between QCT and DEXA.
Lange[23]	Cross-sectional	NR	AS†	84 (53/31)	I: 9 II: 20 III: 21 IV: 32	DEXA: AP LS, TF; SE-QCT: LS	DEXA: osteopenia in 5% and osteoporosis in 9.2%. SE-QCT: osteopenia 11.8%, osteoporosis 30.3%.
Maillefert[24]	Longitudinal 2-yr followup	Consecutive	AS†	54 (35/19)	12.4	DEXA: PA LS, FN	Baseline: FN 39% osteopenic and 11% osteoporotic; LS 39% osteopenic, 17% osteoporotic. Followup: significant bone loss at FN, not at LS; no significant change in proportion of osteopenic and osteoporotic patients.
Mitra[25]	Cross-sectional	Consecutive	AS¥	66 (66/0)	9.85	DEXA: AP LS, FN	Reduced BMD (LS, FN) in AS compared to controls.
Toussirot[26]	Cross-sectional	Consecutive	AS†	71 (49/22)	10.6	DEXA: AP LS, FN	Prevalence (%) of normal BMD, osteopenia and osteoporosis at each site: LS: 53.5, 32.4, 14.1 FN: 73.2, 22.5, 4.3
Ulu[27]	Cross-sectional	Consecutive	AS†	59 (50/9)	11.5	DEXA: PA LS, lat LS, TF	PA LS: osteopenia 51%, osteoporosis 15%. FN: osteopenia 46%, osteoporosis 12%. Lat LS ≤ T score −2.5: 32%.

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Table 1. Continued.

Author	Design	Recruitment	Study Population	N (M/F)	Disease Duration, yrs, mean	BMD Measurement Technique(s)	Result
Ulu[28]	Cross-sectional	Consecutive	AS†	86 (69/17)	11.74	DEXA: PA LS, lat LS, TF, FN	Comparison with control group: FN, TF and lat LS significantly lower in AS patients. No significant difference in PA LS between groups. PA LS significantly higher in late versus early AS.
Van der Weijden[29]	Cross-sectional	Consecutive	SpA¥¥ + IBP: AS 72% uSpA 12% PsA 8% IBD 4% ReA 4%	130 (86/44)	6.3	DEXA: AP LS, PF	Prevalence of low BMD: Osteopenia 28.5% (FN), 30.8% (LS), 37.7% (both) Osteoporosis 2.3% (FN), 7.7% (LS), 8.5% (both). No significant differences in BMD between hip and LS.
Venceviciene[30]	Longitudinal 48-mo followup	Consecutive	SpA¥¥: AS 51% PsA 27% EnA 10% ReA 12%	41 (34/7)	62.2 mos	DEXA: PF	27% of patients had BMD loss over the 48 mos.

Classification criteria for inclusion not reported. $ Chronic lower back pain (LBP), divided into 2 groups – 1. fulfill ASAS criteria; 2. mechanical LBP. † Fulfilling modified New York criteria. * DESIR cohort: a prospective, multicenter French cohort of patients with early IBP suggestive of SpA. †† Symptoms suggestive of axSpA according to local rheumatologist's assessment. ‡ SpA diagnosis made by treating rheumatologist. ‡‡ < 10 yrs duration, no ankylosis, persistent inflammatory disease activity. ¥ modified Schober's test ≥ 5 cm, radiographically normal hips, absent or incipient syndesmophytes. ¥¥ European Spondylarthropathy Study Group criteria. AP: anteroposterior; AS: ankylosing spondylitis; ASAS: Assessment of SpondyloArthritis International Society; axSpA: axial spondyloarthropathy; BMD: bone mineral density; BME: bone marrow edema; DEQCT: dual-energy quantitative computed tomography; DEXA: dual-energy x-ray absorptiometry; EnA: enteropathic arthropathy; FN: femoral neck; HRpQCT: high-resolution peripheral quantitative computed tomography; IBP: inflammatory back pain; lat LS: lateral lumbar spine; LR+: positive likelihood ratio; LS: lumbar spine; mLBP: mechanical lower back pain; MRI: magnetic resonance imaging; nr-axSpA: nonradiographic axial spondyloarthritis; NR: not reported; PA: posteroanterior; PF: proximal femur; pQCT: peripheral QCT; PsA: psoriatic arthropathy; ReA: reactive arthritis; SE-QCT: single-energy QCT; SpA: spondyloarthropathy; SPA: single-photon absorptiometry; TF: total femur; uSpA: undifferentiated SpA; vBMD: volumetric bone mineral density; WB: whole body; IBD: inflammatory bowel disease.

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terior (PA) dual-energy x-ray absorptiometry (DEXA) at the spine and hip, as recommended by the International Society of Clinical Densitometry (ISCD)[32]. However, the hallmark of axSpA is sacroiliitis and spinal damage due to both bony erosion and abnormal bone formation. This can lead to the development of syndesmophytes, perivertebral bone formation, ankylosis of the zygapophyseal joints, and pathologic new bone formation in the ligamentous apparatus. In severe cases, complete fusion of the spine can occur. This extensive osteoproliferation can falsely raise the BMD when PA (conventional) DEXA is used, giving an illusion of reassuringly normal BMD, even in cases where osteoporosis may be present. A study of 73 patients with AS using PA DEXA found that the frequency of low BMD in patients with mild disease was 68.4% in the lumbar spine, but the prevalence dropped to 54.3% in advanced cases[8]. This contrasted with the hip, where the prevalence increased from 51.9% in patients with mild disease to 91.7% in advanced cases. As the disease duration increased, there was a paradoxical rise in lumbar spine BMD, but decline of total hip BMD.

The optimal method to identify BMD loss is under dispute. The literature is conflicted as to whether BMD loss in axSpA is a local or systemic process. Low BMD was significantly more common in 103 patients with AS at femoral neck than at the lumbar spine, measured by DEXA or dual-energy quantitative computed tomography (DEQCT)[19]. However, another study of 71 AS patients with a mean disease duration of 10.6 years found that the prevalence of low BMD was higher than controls at the lumbar spine, but not at the femoral neck[26]. Yet other DEXA studies have shown the central and peripheral skeletons are equally affected by low BMD[21].

In view of the limitations of traditional PA DEXA, alternative methods to assess BMD in patients with axSpA are clearly indicated. QCT has the advantage of measuring volumetric BMD (vBMD) without being affected by cortical artifacts, a technique that is highly attractive for patients with AS. In a study of 69 patients with AS, investigators found that QCT of the lumbar spine detected significantly more cases of osteoporosis and osteopenia than anteroposterior (AP) DEXA[20]. High-resolution peripheral QCT (HRpQCT), a newer technique that provides knowledge about bone microarchitecture, was also performed[20]. This demonstrated lower vBMD in the distal radius and tibia of patients with AS than in controls. It also demonstrated strong correlations between central and peripheral trabecular vBMD[20], suggesting a systemic pattern of bone loss.

Although QCT of the lumbar spine has advantages over PA DEXA, the radiation dose associated with it makes safer methods desirable. Lateral DEXA scanning of the lumbar spine exclusively examines the BMD of the trabecular component of the bodies of the vertebrae, thus excluding the cortical-rich posterior components of the spine. Because osteoproliferation predominantly affects the cortical aspect of the spine, lateral DEXA should, in theory, be less affected by the changes that occur in the spine of patients with axSpA. Similar to axSpA, the degenerative changes that occur in the spine with age can also cause overestimation of BMD when using PA DEXA[33]. Lateral DEXA has been shown to identify more patients with age-related bone loss than AP conventional DEXA, in both men and women[33]. Previously, lateral DEXA was performed with the patient lying on their side. However, precision was very low and was deemed too insensitive to have any clinical use. The modern method to acquire lateral DEXA scans is that the arm of the DEXA scan is rotated 90° and is obtained without the patient moving. Supine lateral measurements have been shown to offer similar precision to the standard AP DEXA scan[34].

In AS, lumbar spine BMD was significantly lower with lateral DEXA measurement than with AP projection and significantly more cases of osteoporosis were detected (26% vs 16%; $p < 0.001$)[21]. Therefore, lateral DEXA is a promising tool to identify cases of osteoporosis without being affected by the osteoproliferation associated with axSpA.

Trabecular bone score (TBS) is a recently emerged tool obtained by reanalyzing AP lumbar spine DEXA images and evaluating variations in grey-level texture from pixel to pixel. It can distinguish between different microarchitectures that have the same bone density. The higher the TBS, the stronger the microarchitecture of the bone, which in turn is more resistant to fracture. In the general population, TBS is related to fracture risk[35]. There is a paucity of literature on axSpA, but 1 study showed that TBS was not influenced by syndesmophytes in contrast to AP DEXA measurement of the spine, although it did not identify prevalent fractures[36]. More research is needed to determine whether TBS would be a useful tool in patients with axSpA.

Factors Associated with Low BMD

The risk factors for reduced BMD are well outlined in the general population. Unfortunately, evidence supporting patient and disease characteristics associated with bone loss in axSpA is inconsistent (Supplementary Table 1, available from the authors on request) and largely based on cross-sectional studies, where causal links are harder to establish.

Differences between the sexes. In the general population, women have a much higher risk of osteoporosis than men[37]. However, the current literature is conflicted regarding a male/female effect on BMD loss in patients with axSpA (Supplementary Table 1, available from the authors on request). Cross-sectional studies of AS patients with conventional DEXA measurements showed that male sex was associated with a lumbar or hip BMD T score of ≤ –1 SD[6] and the prevalence of low BMD in the spine was higher in men[27]. However, a 4-year longitudinal study[15] of patients with early AS demonstrated no sex effect on predicting bone loss, again as measured by conventional DEXA. A further longitudinal study of patients with axSpA, of whom 51% had

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AS, also found no sex effect on bone loss, although only BMD measurements of hips were performed[30].

Perhaps this lack of effect is a bias owing to the historic underrecognition of axSpA in females and their subsequent underrepresentation in studies. As this disease is increasingly diagnosed in women, more robust studies with equal spread among men and women may answer this question more definitively. However, because the existing literature has an excess of men, it highlights that low BMD does indeed affect men with axSpA, a critically important point, because men and osteoporosis are not often thought of in the same sentence.

Disease duration. There is no consensus on the effect of disease duration on BMD, as illustrated in Supplementary Table 1 (available from the authors on request). As outlined earlier, BMD loss begins early in the disease course of both nr-axSpA and AS[5,8,29]. However, increasing disease duration is not consistently associated with worsening BMD[26,27], but this likely reflects the difficulty in assessing BMD in late disease, owing to the higher prevalence of structural damage. The difference between PA lumbar spine and hip T scores measured by DEXA increases in tandem with disease duration[6]. However, lateral DEXA measurements appear to correlate better with disease duration[28].

BASDAI. One of the most frequently used tools to assess disease activity is the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), a patient-reported outcome (PRO)[38]. Many DEXA studies, both cross-sectional[21] and longitudinal[15], have found no correlation between BMD and BASDAI. There are a few notable exceptions, however. One cross-sectional study measured BMD of the lumbar spine with QCT[39] and found a higher mean BASDAI in patients with osteoporosis of the spine than without (8 vs 4; $p < 0.05$). Conversely, Arends, *et al*[6] found that when patients with AS were categorized as low BMD if the T score of the lumbar spine or hip was ≤ –1 SD by DEXA, then a lower BASDAI was independently associated with low BMD (hip or spine).

A disadvantage of BASDAI is that it reflects the current disease activity and does not detect periods of potentially prolonged active disease in the past. Therefore, it is possible that a once-off calculation of BASDAI cannot predict BMD loss, but that the average score over time would be more useful. This hypothesis is supported by a 4-year longitudinal DEXA study of patients with SpA[30], in which the patient group with more BMD loss had a higher average BASDAI score than those without BMD loss.

BASMI. The Bath Ankylosing Spondylitis Metrology Index (BASMI) is a validated tool to objectively assess spinal mobility[40]. Several cross-sectional studies have found an association between higher total BASMI and low BMD (Supplementary Table 1, available from the authors on request). A longitudinal study[30] demonstrated that over 4 years, a deterioration in lateral flexion and intermalleolar distance readings of patients with SpA was associated with BMD loss at the hips (lumbar spine not assessed).

Inflammatory markers. Many studies (Supplementary Table 1), both longitudinal and cross-sectional, including DEXA and QCT, have found an association between higher C-reactive protein or erythrocyte sedimentation rate and lower BMD. However, to date, whether the addition of laboratory variables to PRO, in scores such as the Ankylosing Spondylitis Disease Activity Score, improves the predictive value of low BMD has not been investigated.

Radiological severity. From the Outcome Assessments in AS International Study cohort[41], we know that more active disease is associated with progressive radiographic spinal change, as measured by the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) or the Bath AS Radiological Index (BASRI). The effect of radiographic damage on BMD is less clear (Supplementary Table 1, available from the authors on request). In the presence of syndesmophytes, more patients with AS had low BMD when measured by DEXA of femoral neck or DEQCT of lumbar spine than when AP DEXA of the spine was used[19]. After 10 years of disease duration, AP DEXA of the lumbar spine did not detect any cases of osteoporosis, and DEQCT at lumbar spine and DEXA of femoral neck were used instead. Another study using QCT to assess BMD of the lumbar spine showed that increasing mSASSS correlated significantly with a lower volumetric BMD in the lumbar spine[20]. In that study, peripheral bone microarchitecture, as measured by HRpQCT of the radius and tibia, was also worse in patients with more advanced structural damage, a finding supported by Nigil Haroon, *et al*[17].

Vertebral Fractures

The clinical significance of osteoporosis is in the increased risk of fractures. In the general population, this risk is extremely well outlined[37]. It is less well defined in axSpA.

Multiple studies have shown that AS involves an increased risk of vertebral fractures (VF) compared to age- and sex-matched controls (Table 2[42,43,44,45,46,47]). It is also known that VF in patients with AS have a higher rate of complications, including devastating neurological outcomes[48], than the general population. However, studies have demonstrated a wide variation in prevalence, anything up to 32% (Table 2). A large primary care–based case-control study in the United Kingdom[47] selected 231,436 cases of fracture, vertebral and nonvertebral, recorded in the General Practice Research Database and matched with 231,362 controls. Patients with AS had an increased risk of clinical VF than controls, even when corrected for potential confounders (OR 3.26, 95% CI 1.51–7.02). However, the risk of peripheral fractures in patients with AS was not increased, except in a subset that had a concomitant diagnosis of inflammatory bowel disease (OR 2.79, 95% CI 1.10–7.08). A Swedish-based registry prospective study[46] identified all patients with a primary

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Table 2. Studies outlining prevalence of vertebral fractures in axial spondyloarthritis.

Author	Design	N (M/F)	Study Population	Disease Duration, yrs, mean	Definition of VF	Prevalence of VF (%)	Association with Low BMD
Arends[6]	Cross-sectional	128 (93/35)	AS†	14	Radiographic[A]	20%	No association
Capaci[8]	Cross-sectional	73 (49/24)	AS†	11.8	Radiographic[B]	5.5%	No association
Donnelly[10]	Cross-sectional	87 (62/25)	AS#	M: 16.3, F: 16.6	Radiographic[B]	10.3, n = 9	No reduction in BMD by DEXA of LS, FN, and WB.
Geusens[13]	Cross-sectional	390 (175/215)	SpA‡: 73.3% AS 10.3% PsA 4.6% EnA 11.8% uSpA	10.8	Radiographic[A]	11.8%	Significantly associated with FN BMD: OR 1.38 per 1 SD decrease of T score (95% CI 1.08–1.62)
Ghozlani[14]	Cross-sectional	80 (67/13)	AS†	10.8	Radiographic[A]	18.8%	Associated with reduced BMD and T score at hip site and presence of osteoporosis at any site
Jun[18]	Cross-sectional	68 (68/0)	AS†	68 mo	Radiographic[A]	16.2%	Lower BMD at hip
Klingberg[44]	Cross-sectional	204 (117/87)	AS†	24	Radiographic[A]	11.8%	Patients with VF had significantly lower BMD at all sites compared to patients without a VF
Klingberg[20]	Cross-sectional	69 (69/0)	AS†	23	Radiographic[A]	12%	DEXA: AP and lateral lumbar BMD, lumbar vBMD and BMD of FN, and TH all lower in patients with VF. No difference in forearm DEXA. QCT: lower cortical lumbar vBMD in presence of VF.
Lange[39]	Cross-sectional	58 (38/20)	AS†	17.6	Radiographic[C]	12.1%	All VF had osteoporosis by QCT LS
Maillefert[24]	Longitudinal 2-yr followup	54 (35/19)	AS†	12.4	Radiographic[A]	3.7%	NR
Mitra[25]	Cross-sectional	66 (66/0)	AS¥	9.85	Radiographic[B]	16.7% vs 2.6% of controls (OR 5.92)	No correlation between BMD of LS or FN and VF
Montala[45]	Cross-sectional	176 (138/38)	AS†	22.5	Radiographic[A]	32.4%	NR
Robinson[46]	Prospective	17764 (M/F NR)	AS††	NR	Clinical[D]	4.1%, n = 724 Increased proportion of VF in admitted patients from 0.82% in 1987 to 11.3% in 2008	NR
Toussirot[26]	Cross-sectional	71 (49/22)	AS†	10.6	Radiographic[A]	1.4%	NR
Ulu[27]	Cross-sectional	59 (50/9)	AS†	11.5	Radiographic[E]	30.6%	VF associated with osteoporosis by lat LS DEXA
Vosse[47]	Case-control	758 (442/316)	AS†	NR	Clinical[G]	4.5%	NR

† Fulfilling modified New York criteria. # Classification criteria for inclusion not reported. ‡ SpA diagnosis made by treating rheumatologist. ¥ Modified Schober's test ≥ 5 cm. radiographically normal hips, absent or incipient syndesmophytes. †† ICD code of AS in Swedish National Hospital Discharge Registry. A: morphometric VF on radiographs, Genant[42] classification; AS: ankylosing spondylitis; B: morphometric VF on radiographs, McCloskey[43] classification; BMD: bone mineral density; C: morphometric VF on radiographs, vertebral height (thoracic/lumbar spine) height decrease > 15%; D: discharge diagnosis; E: morphometric VF on radiographs, vertebral height (thoracic/lumbar spine) height decrease > 20%; DEXA: dual-energy x-ray absorptiometry; EnA: enteropathic arthropathy; FN: femoral neck; G: VF diagnosis in General Practice Research Database, computerized records of sample of general practitioners in the United Kingdom; LS: lumbar spine; lat LS: lateral LS; NR: not reported; PsA: psoriatic arthropathy; QCT: quantitative computed tomography; SpA: spondyloarthropathy; TH: total hip; TS: thoracic spine; uSpA: undifferentiated SpA; vBMD: volumetric BMD; VF: vertebral fracture; WB: whole body; AP: anteroposterior.

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discharge diagnosis of VF and concomitant diagnosis of AS admitted between 1987 and 2008 and demonstrated a prevalence of 4.1% for clinical VF among patients with AS, with the proportion of fractures increasing throughout the 22 years of the study. However, registry-based data may underestimate the true prevalence of VF because VF do not always come to clinical attention, and prevalence on radiographic studies is much higher (Table 2).

The reason for the excess risk of VF in this population has not yet been fully elucidated (Supplementary Table 2, available from the authors on request). Cross-sectional studies demonstrated that radiographic detection of VF was correlated with radiological severity of AS, by mSASSS (OR 1.17, 95% CI 1.05–1.3)[14] and BASRI (OR 1.25, 95% CI 1.12–1.39)[45]. BMD may also play a role in the excess risk of VF in patients with AS, as demonstrated by significant correlations between radiographic VF and BMD at all sites measured by DEXA (femoral neck, total hip, lateral lumbar BMD, radius and AP lumbar BMD)[44]. However, in another study, only hip and lateral lumbar spine BMD were significantly lower in the radiographic VF group than in those without fractures[28], with no correlation with AP lumbar spine BMD measurement. Yet other studies have shown no correlation between VF and BMD[10]. A study of 390 patients with axSpA found an increased risk of radiographic VF with lower femoral neck T scores[13].

Low BMD is unlikely to fully explain the excess risk of VF, and decreased bone strength may play a role. HRpQCT of the distal radius and tibia demonstrated that patients with AS had worse microarchitecture (lower cortical and total vBMD, reduced cortical thickness, increased cortical porosity) than patients without AS, despite there being no difference in BMD by DEXA between groups at either the radius or lumbar spine[17]. In another study, male AS patients with VF demonstrated significantly worse peripheral bone microarchitecture (as measured by HRpQCT of the distal radius and ulna) than AS patients without a VF[20].

Although the cause of VF is likely multifactorial, until our assessment techniques for detecting low BMD in AS are improved and standardized, it will be difficult to determine exactly what role BMD plays in the excess risk of VF that exists in this population.

EULAR Guidelines

In 2015, the European League Against Rheumatism (EULAR) published guidelines regarding imaging in axSpA[49] that acknowledged the influence of radiographic change on evaluating BMD. This led to the recommendation that hip and AP DEXA be used in patients without syndesmophytes on conventional radiography. In patients with syndesmophytes, hip DEXA should be used, supplemented by either lateral DEXA or QCT. They also recommended further research to determine which form of imaging provides the best clinical usefulness for the diagnosis and monitoring of low BMD in patients with axSpA.

These guidelines highlight the issue of low BMD in patients with axSpA, a critically important step considering that only 31.6% of rheumatologists indicated that assessing for osteoporosis was part of their routine management of patients with AS[50]. However, the guidelines are limited by the lack of evidence available. BMD loss tends to be a progressive process, particularly if untreated, and thus requires serial monitoring. ISCD guidelines state that the same machine should be used to monitor patients for BMD loss to allow for accurate comparisons[32]. However, inherent to axSpA is the progression of structural damage[41]. Therefore, if EULAR guidelines are strictly followed, AP DEXA will be used in early disease, whereas lateral DEXA or QCT will be used in later disease, which will not allow accurate comparison of BMD. Clearly, having a guideline that recommends one method of BMD assessment in the early stages of the disease and a different one in the later, more structurally advanced stages is less than ideal.

The inherent paradox of osteoproliferation and osteoporosis in axSpA hinders clinicians in accurately managing the bone loss that occurs in this population. It is largely undisputed that low BMD occurs in axSpA, but much more work needs to be done. The most pressing problem is the lack of a standardized and accurate method to detect low BMD in this population. This needs to be clarified, then validated in axSpA, to prevent both under- and overdiagnosis of osteoporosis in axSpA. Without this method, it will remain difficult to accurately define the extent of the problem, as well as to determine predictive factors, consequences, and the effect of treatment on BMD in axSpA.

REFERENCES

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. JAMA 2001;285:785-95.
2. Hauser B, Riches PL, Wilson JF, Horne AE, Ralston SH. Prevalence and clinical prediction of osteoporosis in a contemporary cohort of patients with rheumatoid arthritis. Rheumatology 2014;53:1759-66.
3. Huber AM, Ward LM. The impact of underlying disease on fracture risk and bone mineral density in children with rheumatic disorders: A review of current literature. Semin Arthritis Rheum 2016; 46:49-63.
4. Chandran S, Aldei A, Johnson SR, Cheung AM, Salonen D, Gladman DD. Prevalence and risk factors of low bone mineral density in psoriatic arthritis: A systematic review. Semin Arthritis Rheum 2016;46:174-82.
5. Akgol G, Kamanli A, Ozgocmen S. Evidence for inflammation-induced bone loss in non-radiographic axial spondyloarthritis. Rheumatology 2014;53:497-501.
6. Arends S, Spoorenberg A, Bruyn GA, Houtman PM, Leijsma MK, Kallenberg CG, et al. The relation between bone mineral density, bone turnover markers, and vitamin D status in ankylosing spondylitis patients with active disease: a cross-sectional analysis. Osteoporos Int 2011;22:1431-9.
7. Briot K, Dumez A, Paternotte S, Miceli-Richard C, Dougados M, Roux C. Bone oedema on MRI is highly associated with low bone

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mineral density in patients with early inflammatory back pain: results from the DESIR cohort. Ann Rheum Dis 2013;72:1914-9.
8. Capaci K, Hepguler S, Argin M, Tas I. Bone mineral density in mild and advanced ankylosing spondylitis. Yonsei Med J 2003; 44:379-84.
9. Devogelaer JP, Maldague B, Malghem J, Nagant de Deuxchaisnes C. Appendicular and vertebral bone mass in ankylosing spondylitis. A comparison of plain radiographs with single- and dual-photon absorptiometry and with quantitative computed tomography. Arthritis Rheum 1992;35:1062-7.
10. Donnelly S, Doyle DV, Denton A, Rolfe I, McCloskey EV, Spector TD. Bone mineral density and vertebral compression fracture rates in ankylosing spondylitis. Ann Rheum Dis 1994;53:117-21.
11. El Maghraoui A, Tellal S, Chaouir S, Lebbar K, Bezza A, Nouijai A, et al. Bone turnover markers, anterior pituitary and gonadal hormones, and bone mass evaluation using quantitative computed tomography in ankylosing spondylitis. Clin Rheumatol 2005;24:346-51.
12. Forien M, Molto A, Etcheto A, Dougados M, Roux C, Briot K. Bone mineral density in patients with symptoms suggestive of spondyloarthritis. Osteoporos Int 2015;26:1647-53.
13. Geusens P, De Winter L, Quaden D, Vanhoof J, Vosse D, van den Bergh J, et al. The prevalence of vertebral fractures in spondyloarthritis: relation to disease characteristics, bone mineral density, syndesmophytes and history of back pain and trauma. Arthritis Res Ther 2015;17:294.
14. Ghozlani I, Ghazi M, Nouijai A, Mounach A, Rezqi A, Achemlal L, et al. Prevalence and risk factors of osteoporosis and vertebral fractures in patients with ankylosing spondylitis. Bone 2009; 44:772-6.
15. Gratacos J, Collado A, Pons F, Osaba M, Sanmarti R, Roque M, et al. Significant loss of bone mass in patients with early, active ankylosing spondylitis: a followup study. Arthritis Rheum 1999;42:2319-24.
16. Grazio S, Kusic Z, Cvijetic S, Grubisic F, Balenovic A, Nemcic T, et al. Relationship of bone mineral density with disease activity and functional ability in patients with ankylosing spondylitis: a cross-sectional study. Rheumatol Int 2012;32:2801-8.
17. Nigil Haroon N, Szabo E, Raboud JM, McDonald-Blumer H, Fung L, Josse RG, et al. Alterations of bone mineral density, bone microarchitecture and strength in patients with ankylosing spondylitis: a cross-sectional study using high-resolution peripheral quantitative computerized tomography and finite element analysis. Arthritis Res Ther 2015;17:377.
18. Jun JB, Joo KB, Her MY, Kim TH, Bae SC, Yoo DH, et al. Femoral bone mineral density is associated with vertebral fractures in patients with ankylosing spondylitis: a cross-sectional study. J Rheumatol 2006;33:1637-41.
19. Karberg K, Zochling J, Sieper J, Felsenberg D, Braun J. Bone loss is detected more frequently in patients with ankylosing spondylitis with syndesmophytes. J Rheumatol 2005;32:1290-8.
20. Klingberg E, Lorentzon M, Gothlin J, Mellstrom D, Geijer M, Ohlsson C, et al. Bone microarchitecture in ankylosing spondylitis and the association with bone mineral density, fractures, and syndesmophytes. Arthritis Res Ther 2013;15:R179.
21. Klingberg E, Lorentzon M, Mellstrom D, Geijer M, Gothlin J, Hilme E, et al. Osteoporosis in ankylosing spondylitis - prevalence, risk factors and methods of assessment. Arthritis Res Ther 2012;14:R108.
22. Korkosz M, Gasowski J, Grzanka P, Gorczowski J, Pluskiewicz W, Jeka S, et al. Baseline new bone formation does not predict bone loss in ankylosing spondylitis as assessed by quantitative computed tomography (QCT): 10-year follow-up. BMC Musculoskelet Disord 2011;12:121.
23. Lange U, Kluge A, Strunk J, Teichmann J, Bachmann G. Ankylosing spondylitis and bone mineral density—what is the ideal tool for measurement? Rheumatol Int 2005;26:115-20.
24. Maillefert JF, Aho LS, El Maghraoui A, Dougados M, Roux C. Changes in bone density in patients with ankylosing spondylitis: a two-year follow-up study. Osteoporos Int 2001;12:605-9.
25. Mitra D, Elvins DM, Speden DJ, Collins AJ. The prevalence of vertebral fractures in mild ankylosing spondylitis and their relationship to bone mineral density. Rheumatology 2000;39:85-9.
26. Toussirot E, Michel F, Wendling D. Bone density, ultrasound measurements and body composition in early ankylosing spondylitis. Rheumatology 2001;40:882-8.
27. Ulu MA, Batmaz I, Dilek B, Cevik R. Prevalence of osteoporosis and vertebral fractures and related factors in patients with ankylosing spondylitis. Chin Med J 2014;127:2740-7.
28. Ulu MA, Cevik R, Dilek B. Comparison of PA spine, lateral spine, and femoral BMD measurements to determine bone loss in ankylosing spondylitis. Rheumatol Int 2013;33:1705-11.
29. van der Weijden MA, van Denderen JC, Lems WF, Heymans MW, Dijkmans BA, van der Horst-Bruinsma IE. Low bone mineral density is related to male gender and decreased functional capacity in early spondylarthropathies. Clin Rheumatol 2011;30:497-503.
30. Vencevičienė L, Butrimienė I, Vencevičius R, Sadauskienė E, Kasiulevičius V, Šapoka V. Factors associated with bone mineral density loss in patients with spondyloarthropathies: A 4-year follow-up study. Medicina 2015;51:272-9.
31. Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68:777-83.
32. Schousboe JT, Shepherd JA, Bilezikian JP, Baim S. Executive summary of the 2013 International Society for Clinical Densitometry Position Development Conference on bone densitometry. J Clin Densitom 2013;16:455-66.
33. Finkelstein JS, Cleary RL, Butler JP, Antonelli R, Mitlak BH, Deraska DJ, et al. A comparison of lateral versus anterior-posterior spine dual energy x-ray absorptiometry for the diagnosis of osteopenia. J Clin Endocrinol Metab 1994;78:724-30.
34. Blake GM, Jagathesan T, Herd RJ, Fogelman I. Dual X-ray absorptiometry of the lumbar spine: the precision of paired anteroposterior/lateral studies. Br J Radiol 1994;67:624-30.
35. Harvey NC, Gluer CC, Binkley N, McCloskey EV, Brandi ML, Cooper C, et al. Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice. Bone 2015;78:216-24.
36. Wildberger L, Boyadzhieva V, Hans D, Stoilov N, Rashkov R, Aubry-Rozier B. Impact of lumbar syndesmophyte on bone health as assessed by bone density (BMD) and bone texture (TBS) in men with axial spondyloarthritis. Joint Bone Spine 2017;84:463-6.
37. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int 2006;17:1726-33.
38. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286-91.
39. Lange U, Teichmann J, Strunk J, Muller-Ladner U, Schmidt KL. Association of 1.25 vitamin D3 deficiency, disease activity and low bone mass in ankylosing spondylitis. Osteoporos Int 2005; 16:1999-2004.
40. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol 1994;21:1694-8.
41. Ramiro S, van der Heijde D, van Tubergen A, Stolwijk C, Dougados M, van den Bosch F, et al. Higher disease activity leads to more

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structural damage in the spine in ankylosing spondylitis: 12-year longitudinal data from the OASIS cohort. Ann Rheum Dis 2014;73:1455-61.
42. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8:1137-48.
43. McCloskey EV, Spector TD, Eyres KS, Fern ED, O'Rourke N, Vasikaran S, et al. The assessment of vertebral deformity: a method for use in population studies and clinical trials. Osteoporos Int 1993;3:138-47.
44. Klingberg E, Geijer M, Gothlin J, Mellstrom D, Lorentzon M, Hilme E, et al. Vertebral fractures in ankylosing spondylitis are associated with lower bone mineral density in both central and peripheral skeleton. J Rheumatol 2012;39:1987-95.
45. Montala N, Juanola X, Collantes E, Munoz-Gomariz E, Gonzalez C, Gratacos J, et al. Prevalence of vertebral fractures by semiautomated morphometry in patients with ankylosing spondylitis. J Rheumatol 2011;38:893-7.
46. Robinson Y, Sanden B, Olerud C. Increased occurrence of spinal fractures related to ankylosing spondylitis: a prospective 22-year cohort study in 17,764 patients from a national registry in Sweden. Patient Saf Surg 2013;7:2.
47. Vosse D, Landewé R, van der Heijde D, van der Linden S, van Staa TP, Geusens P. Ankylosing spondylitis and the risk of fracture: results from a large primary care-based nested case-control study. Ann Rheum Dis 2009;68:1839-42.
48. Westerveld LA, Verlaan JJ, Oner FC. Spinal fractures in patients with ankylosing spinal disorders: a systematic review of the literature on treatment, neurological status and complications. Eur Spine J 2009;18:145-56.
49. Mandl P, Navarro-Compan V, Terslev L, Aegerter P, van der Heijde D, D'Agostino MA, et al. EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. Ann Rheum Dis 2015;74:1327-39.
50. Bessant R, Harris C, Keat A. Audit of the diagnosis, assessment, and treatment of osteoporosis in patients with ankylosing spondylitis. J Rheumatol 2003;30:779-82.

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MEASURING BONE DENSITY IN AXIAL SPONDYLOARTHROPATHY: TIME TO TURN THINGS ON THEIR SIDE?

Journal:	*Arthritis Care and Research*
Manuscript ID	ACR-19-0522
Wiley - Manuscript type:	Original Article
Date Submitted by the Author:	28-May-2019
Complete List of Authors:	Fitzgerald, Gillian; Trinity College Dublin, Medicine; St James's Hospital , Rheumatology Anachebe, Tochukwu; St. James's Hospital, Rheumatology McCarroll, Kevin; St. James's Hospital, Medicine for the Elderly O'Shea, Finbar; St James's Hospital, Rheumatology
Key Words: Please choose key words for your manuscript. Choosing the best match of the journal's keywords to your work will likely result in better match to reviewers with expertise in your interest area. It may also help to speed the review process.:	Ankylosing Spondylitis (AS), Bone Density, Dual Energy X-Ray Absorptiometry (DEXA)
Optional Terms: You have the option to add additional key words that are not on the journal's list to more specifically categorize your submission.:	axial spondyloarthropathy

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MEASURING BONE DENSITY IN AXIAL SPONDYLOARTHROPATHY: TIME TO TURN THINGS ON THEIR SIDE?

Running head: Measuring bone density in axSpA

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Funding: This work was supported by AbbVie pharmaceuticals through the Bresnihan-Molloy Scholarship to GF from the Royal College of Physicians of Ireland. The funders had no role in the design of the study, collection of the data, analysis and interpretation of the data or any part of manuscript preparation.

Word count: 3087

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ABSTRACT

Objective

Osteoporosis in axial spondyloarthropathy (axSpA) is difficult to accurately diagnose due to osteoproliferation of the spine interfering with conventional (posteroanterior, PA) dual-energy x-ray absorptiometry (DXA). This study compares PA and lateral projections of DXA when assessing bone mineral density (BMD) of the spine and investigates the impact of osteoproliferation on PA DXA.

Methods

In this cross-sectional study, structured standardised assessments collected demographic, clinical, laboratory and radiographic data. DXA assessed BMD of the spine using PA and lateral projections. Hip BMD was assessed in the usual manner. World Health Organisation (WHO) criteria assessed prevalence of low BMD. Performance of lateral in place of PA DXA in diagnosing low BMD was investigated. SPSS was used for statistical analysis.

Results

A total of 100 patients had paired PA and lateral DXA studies: 78% male, mean (SD) age 52 (12) years. BMD of the spine measured by PA projection was significantly higher than BMD measured by lateral projection (mean difference 0.34 g/cm^2, 95% CI 0.30 to 0.37). More patients had low BMD with lateral compared to PA projection (47% versus 16%, p=0.01). At the hip, 34% of patients had low BMD. Disease duration, body mass index (BMI) and radiographic severity independently predicted a difference between PA and lateral measurements of the spine.

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Conclusion

Lateral DXA of the spine is unaffected by osteoproliferation of the spine in axSpA and detects significantly more cases of low BMD than conventional PA DXA. Lateral DXA should be included in BMD assessment of patients with axSpA.

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INNOVATIONS

- We demonstrated that osteoproliferation in axSpA interferes with conventional DXA assessment of bone mineral density of the spine, risking under-recognition of osteoporosis in this population.
- Lateral DXA is a technique that assesses trabecular bone of the vertebra, avoids osteoproliferation of the spine and identifies more low bone density than conventional DXA.

SIGNIFICANCE

- We suggest lateral DXA of the spine should be added to the bone density assessment of all axSpA patients.

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Axial spondyloarthropathy (axSpA) is a chronic inflammatory arthritis, predominantly affecting the sacroiliac joints and spine. The Assessment in SpondyloArthritis International Society (ASAS)-COMOSPA study recently demonstrated a high prevalence of comorbidity in patients with axSpA (1), noting osteoporosis as the most prevalent, affecting 13% of the surveyed population. Other investigators have similarly reported a high prevalence of low bone mineral density (BMD), although figures vary widely, ranging from 4% to greater than 50% (2-5).

Vertebral fracture prevalence is also increased in patients with axSpA (6-8), with mortality and potential for devastating neurological outcomes higher than the general population (9, 10). The reason for the excess vertebral fracture risk is unclear, with the relationship between osteoporosis and vertebral fractures not as clearly defined as in the general population (11-14). The risk factors for low BMD are also less studied in the axSpA population (5), and there is limited data available to recommend treatment strategies to maintain or improve BMD (15, 16), in contrast to strategies that are well delineated in the general population (17).

Much of the difficulty with estimating BMD of the spine in axSpA is related to the inherent pathophysiology of axSpA, a process which remains incompletely understood (18). It is thought that inflammation of the vertebrae over time can result in erosion and ultimately osteoproliferation at the attachment sites of spinal ligaments into the vertebrae, termed syndesmophytes, with complete ankylosis as its most extreme form (19, 20). Conventional dual-energy x-ray absorptiometry (DXA) of the lumbar spine assesses BMD in a posterior-anterior (PA) direction (21). In axSpA, conventional DXA is unable to distinguish between BMD of the vertebral body and osteoproliferation. BMD of the spine can thus be over-

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estimated when conventional DXA is used, producing an illusion of reassuringly normal BMD, when significant bone loss may have occurred (22).

A technique where assessment of the spine is unaffected by osteoproliferation is needed to better understand the epidemiology, and ultimately consequences, of low BMD in axSpA patients. Lateral DXA scanning examines the vertebral body from the side, almost exclusively measuring trabecular bone and avoiding much of the osteoproliferation that interferes with BMD assessment of the spine when using conventional DXA (23). Modern DXA scanners allow lateral scans to be performed in the supine position and have similar precision to PA scans (24). Lateral DXA of the spine in axSpA has been shown in a small number of studies to detect more cases of low BMD than conventional DXA (13, 25, 26). The International Society of Clinical Densitometry (ISCD) recommend that a diagnosis of osteoporosis is made if the T-score of the lumbar spine, total hip or femoral neck is -2.5 or less (21). Previous studies investigating the use of lateral DXA in axSpA have been limited by lack of reference databases, prohibiting calculation of T-scores. Therefore, the utility of substituting lateral DXA in place of conventional PA DXA to improve the detection of low BMD when combined with hip data is unknown.

The aims of this study are to:

1. compare the assessment of BMD of the spine of axSpA patients using PA and lateral projections of DXA
2. determine if substituting lateral in place of PA spine BMD measurements when combining with hip measurements to assess for low BMD improves performance
3. determine variables (patient and disease-related) that affect the accuracy of conventional DXA.

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PATIENTS AND METHODS

Population

This is an observational cross-sectional twin-centre study. Patients were consecutively recruited between April and December 2017 from dedicated spondylitis and general rheumatology clinics in St. James's Hospital and Tallaght University Hospital, Dublin, Ireland, if they were adults (≥ 18 years of age) and fulfilled the ASAS criteria for axSpA. Patients were excluded if they were pregnant, actively trying to conceive, breast-feeding, under 18 or had a history of cognitive impairment which precluded informed consent. Additionally, patients were identified from the axSpA database and contacted over telephone using a script to invite participation. All data collection was performed in St. James's Hospital. The study was approved by the joint Tallaght University Hospital/St. James's Hospital Research Ethics Committee. Written informed consent was obtained from each participating subject.

Demographic and disease-related data

Data collection was performed according to a standardised protocol:

- Demographics: gender, age, ethnicity, smoking status (never, past, current), employment status.
- Disease characteristics: symptom duration, age at diagnosis, extra-articular manifestations (uveitis, inflammatory bowel disease, psoriasis), SpA features (enthesitis, dactylitis, peripheral arthritis), co-morbidities, treatment (axSpA and osteoporosis) history, osteoporosis risk factors, fracture history.

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- Physical examination: tragus-to-wall, cervical rotation, modified Schober's test, lateral flexion, intermalleolar distance, chest expansion – performed according to a standardised technique (27). Height was measured to the nearest 0.1 cm, weight in kilograms (kg). Body mass index (BMI), expressed in kg/m^2, was defined as body weight divided by square of body height.
- Laboratory measurements: routine bloods (full blood count, renal profile, bone profile, liver profile, erythrocyte-sedimentation rate (ESR), C-reactive protein (CRP), parathyroid hormone (PTH), vitamin D) were collected on the same day of assessment and analysed using standard laboratory techniques. Human leucocyte antigen (HLA) B-27 antigen was reported as positive or negative.

Outcome measures

The following patient-reported outcome measures were collected:

- Bath AS Disease Activity Index (BASDAI) (28)
- Bath AS Functional Index (BASFI) (29)
- AS Quality of Life (ASQoL) (30)
- Bath AS Patient Global score(BAS-G) (31)
- Health Assessment Questionnaire (HAQ) (32)

Ankylosing Spondylitis Disease Activity Score (ASDAS) and Bath AS Metrology Index (BASMI) were calculated (27, 33). The modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) was calculated using lateral lumbar and cervical spine x-rays, assessing radiographic damage

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from a scale of 0-72 (34). Antero-posterior pelvic x-rays were performed to grade sacroiliitis according to the modified New York criteria (35).

Bone mineral density

BMD was assessed using a Hologic Horizon A DXA scanner. Lumbar spine BMD was measured in PA (L1-4) and lateral (L2-4) projections. Conventional femoral neck and total hip BMD measurements were performed. Quality control was performed in accordance with international recommendations (21). BMD was expressed as g/cm^2. The NHANES III data was used as reference for hip T-scores. The manufacturer's database was used as the reference standard for the lumbar spine, in line with ISCD positions (36). Z-scores were not available for lateral spine DXA for male patients. Osteoporosis was defined according to the World Health Organisation (WHO) for post-menopausal women and men over the age of 50 years as normal if T score >= -1, osteopenia if between -1 and -2.5 and osteoporosis if <=-2.5 (37). For pre-menopausal women and men under the age of 50 years, a Z score of <-2 was considered to represent low BMD. When calculating prevalence of osteoporosis and osteopenia, only postmenopausal women and men over the age of 50 were included, in accordance with the ISCD positions (36).

Bias

Selection bias was minimised by using clinic and database recruitment, to ensure a representative the study sample. Non-responders via phone recruitment were phoned on separate occasions at different times/days to minimise non-response bias. Volunteer bias

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was minimised by keeping the data collection time short and offering flexible appointment times. Bias in data collection was minimised by giving patients questionnaires to fill out themselves to avoid under-reporting of certain behaviours. The questionnaires were reviewed by the investigator to ensure completeness of data entry while the patient was there. Assessment bias was minimised by all data collection being performed by 2 trained investigators (GF and TA).

Statistical methods

Descriptive statistics are presented as frequencies with percentages, mean with standard deviation (SD) or median with 25^{th} and 75^{th} percentiles as appropriate. Differences between PA and lateral BMD of the spine were assessed using paired T-tests. Relationships between continuous variables were assessed using Pearson's correlation coefficients (r) or Spearman's correlation coefficients (rho) as appropriate. Independent 2-tailed T-tests were used to explore differences between groups in continuous data. Chi-square tests were used to compare categorical variables.

The difference between PA and lateral BMD was calculated (PA minus lateral BMD) and expressed in g/cm^2. We developed a model to predict the difference between PA and lateral BMD (dependent variable) from independent variables. Univariable analysis was performed to identify variables associated with the dependent variable and tested in simple linear regression. All variables with a p value of <0.1 in crude analysis were entered in the regression model, along with clinically relevant variables. Normality of residuals and multicollinearity were assessed. IBM SPSS version 24 was used for statistical analysis. A p-value of <0.05 was considered statistically significant.

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RESULTS

Baseline characteristics

A total of 110 patients were recruited between May 2017 and January 2018, of whom 10 were unable to have DXA imaging of the spine, thus 100 patients with paired PA and lateral DXA of the lumbar spine were included: 78% (n=78) male, 98% (n=98) Caucasian, median (IQR) age was 52.3 (43.2, 59.4) years, disease duration 23.6 (14.4, 34.9) years and delay to diagnosis 7 (2, 13.5) years. The mean mSASSS was 23.2 (SD 24.7, median 10, IQR 4, 37.3), with 8% (n=8) having a score of 0 and 8% (n=8) having a "bamboo spine". Remaining baseline demographic and clinical characteristics are outlined in table 1. Reported fragility fracture prevalence was low in the cohort (3%).

Measured BMD of spine (PA and lateral projections of DXA) and hip

Mean BMD of spine and hip are outlined in table 1. All measured sites of BMD correlated positively with each other. BMD of the spine measured by PA (conventional) projection correlated positively with age, mSASSS and BASMI, indicating that PA BMD of the spine increased in older patients and patients with higher mSASSS and BASMI scores (table 2). In contrast, BMD of the spine measured by lateral projection showed no correlation with mSASSS or BASMI, and a non-significant inverse correlation with age; similar patterns were found at the hip. Men had higher BMD than women at the spine (both projections) and the hip; smoking status, exposure to biologic treatment, HLA-B27 positivity or presence of osteoporosis risk factors had no impact on BMD (supplementary table 1).

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Comparison of lumbar spine BMD using PA and lateral DXA

BMD of the lumbar spine measured by PA projection is significantly higher than when BMD is measured by lateral projection (mean difference 0.34 g/cm², 95% CI 0.30 to 0.37), as demonstrated in figure 1. The difference between PA and lateral measurements of lumbar spine BMD (PA minus lateral BMD) correlated with age, mSASSS, BASMI, BMI and BASFI (see table 2). This indicates that the older the patient or the more severe the disease, the bigger the difference between the PA (conventional) and the lateral BMD measurement. The difference between PA and lateral BMD of the spine was similar in men and women (mean difference between genders was 0.04 g/cm², 95% CI -0.04 to 0.12). Additionally, there was no correlation between PA and lateral BMD difference and inflammatory markers or vitamin D ($p>0.05$).

Prevalence of low BMD

Fifty-seven patients fulfilled criteria for classification of BMD using T scores (i.e. men ≥ 50 years and post-menopausal women). Of this cohort, 16% had low BMD of the spine when measured by PA DXA, compared to 47% when measured by lateral DXA (chi-square 7.4, $p=0.01$, OR 12.2, 95% CI 1.4 to 106), as outlined in figure 2. At the hip, 34% (n=19) had low BMD at either femoral neck or total hip.

As per the WHO definition (37), hip and spine data was combined to assess for low BMD at any site. When PA spine BMD was combined with hip BMD, 35% (n=20) of patients had low BMD at a minimum of one site. However, when lateral spine BMD was combined with hip

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BMD, 56% (n=32) of patients had low BMD, a statistically significant difference (Chi-square 18.9, df 1, p<0.001).

Z scores for lateral lumbar spine BMD are not available in men, therefore similar data cannot be presented for the remainder of the population.

Prediction of difference between PA and lateral BMD

We developed a model to predict the difference between PA and lateral BMD, as outlined in methods. We additionally controlled for gender and exposure to treatment with biologics. After correcting for multicollinearity, the R^2 of the final model was 0.4 (table 3). Disease duration, BMI and mSASSS remained independent predictors of the difference between PA and lateral BMD of the spine.

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DISCUSSION

Osteoporosis is widely accepted to occur at an increased prevalence in axSpA compared to age- and sex-matched controls. However, accurately assessing BMD of the spine is challenging in axSpA patients due to overestimation that occurs from calcification and osteoproliferation, as we previously outlined in a review of this topic (38).

In this study of 100 axSpA patients, we demonstrated that when directly compared, raw BMD of the spine expressed in g/cm^2 is significantly lower when measured by lateral projection of DXA than by conventional PA DXA, confirming findings by other researchers (25, 39). The clinical significance of BMD is not in the raw BMD expressed in g/cm^2, but in its WHO classification as normal or low BMD using T scores, as it is this which is clearly associated with morbidity and mortality in the general population (40, 41). Previously, the performance of lateral spine DXA in detecting low BMD in axSpA was limited by lack of adequate reference databases to compute T scores (25, 26). In our study, a manufacturer-compiled reference database allowed us to compute T scores (but unfortunately not Z scores) for both men and women. Therefore, we compared the performance of lateral and PA DXA in detecting low BMD according to WHO criteria and found that lateral DXA detected significantly more cases of low BMD (47%) than did PA DXA (16%).

In practice, a diagnosis of low BMD is made if a patient fulfils WHO criteria for either osteopenia or osteoporosis of at least one site of spine or hip (37, 42). Using lateral DXA in place of PA DXA improved our diagnosis of low BMD significantly from 35% to 56%. Had we relied on hip data alone, as advocated by some clinicians (26), only 34% of patients would have received a diagnosis of low BMD. Thus, using lateral DXA in place of PA DXA to assess BMD improves the performance. In the general population, lateral DXA has been shown to

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identify more cases of low BMD than conventional DXA (23, 43). However, to our knowledge, this is the first study in axSpA to show this.

Understanding the reason for the disconnect between PA and lateral DXA is crucial to comprehend why conventional DXA is inaccurate in axSpA. In contrast to the expected decline in BMD that occurs with age in the general population, we demonstrated that PA BMD of the spine increases instead. PA BMD also increased as mSASSS and BASMI increased. This association was not seen when BMD of the spine was measured by lateral DXA, indicating a disconnect between the 2 different methods of measurement of the same site. Hip BMD demonstrated similar results to lateral DXA.

We further explored associations with the difference between PA and lateral DXA. BMI can affect the measurement of BMD due to interference from soft-tissue (44, 45), thus it is appropriate to control for this in models. After controlling for BMI, mSASSS and disease duration remained independent predictors of the difference between PA and lateral DXA of the spine. In simpler terms, after we controlled for BMI, we found that the longer the disease duration and the higher the mSASSS, the bigger was the gap between PA and lateral i.e. the higher the PA and the lower the lateral.

This confirms previous research (39) which similarly demonstrated that the difference between PA and lateral BMD of the spine correlated with mSASSS. This is an important finding, signifying that structural damage in the form of osteoproliferation is interfering with the accuracy of what is currently our "gold standard" technique to assess BMD in axSpA patients (21).

It has been the subject of much debate as to whether osteoporosis in axSpA is localised to the spine or is a more systemic process (39, 46-48). We demonstrated a higher prevalence

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of low BMD at the spine compared to the hip, suggesting the spine is affected to a more significant degree than are the hips. Therefore, it is important that we have a method to accurately assess BMD of the spine, which isn't affected by the severity of disease. We note the interesting results of a recent study published (26) which was the first to examine lateral measurements of the spine longitudinally and unexpectedly found that both lateral and PA BMD increased over time. However, there were no reference values available for lateral BMD measurements in the men, so the authors urge caution with interpretation of this finding.

We would like to acknowledge some limitations. Firstly, this is a cross-sectional study, which prohibits comment on causality – we can merely comment on associations. Secondly, the population is almost exclusively Caucasian, thus caution must be applied when extrapolating results to other ethnicities. Thirdly, we don't have reference values to allow Z scores to be calculated for lateral spine BMD, thus we cannot comment on prevalence of low BMD in men under 50 years and pre-menopausal women. However, the difference between raw BMD values are valid in the entire population. Finally, the clinical significance of osteoporosis is in its associated fracture risk; however, a link between low BMD of the spine and vertebral fractures has not been established definitively in patients with axSpA (49). In this study, the prevalence of fragility fractures was low (3%), therefore we were unable to shed further light on this association. The clinical outcomes of vertebral fractures in patients with axSpA are worse than other populations (9), so it is crucial to understand the role BMD plays in this increased susceptibility. Therefore, future research needs to determine whether there is a correlation between BMD as measured by lateral DXA and vertebral fracture risk.

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This study has many strengths. The patients are well-characterised, with an extensive data set collected. It is a homogenous population, allowing easy extrapolation of the results. All efforts were made to limit sources of bias, thus ensuring our population is representative of the axSpA population.

In summary, lateral DXA of the lumbar spine is a feasible and reliable tool, unaffected by osteoproliferation, which can be used to accurately assess BMD of the spine in patients with axSpA. Continuing to rely on conventional PA DXA risks missing cases of low BMD. Additionally, it prohibits a progression in research to establish a definitive link between vertebral fractures and spinal BMD. Instead, we suggest that lateral DXA should be added to the BMD assessment of patients with axSpA.

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ACKNOWLEDGEMENTS

We thank all the patients who so willingly participated in the study. We would like to also thank Professors David Kane and Ronan Mullan of Tallaght University Hospital for their enthusiastic contribution in providing patients for this study. Additionally, we would like to express our deep gratitude to all the nursing and administrative staff of the Bone Clinic in St. James's Hospital: without their extensive assistance and guidance, this project would never have succeeded.

CONTRIBUTORS

GF was involved in the conception and design of the study, acquisition of data, statistical analysis, interpretation of data and drafting of the manuscript. KMcC and FOS were involved in the conception and design of the study, statistical analysis, interpretation of data and critically revising the manuscript. TA participated in design of the study and data acquisition, statistical analysis and drafting of the manuscript. All authors read and approved the final version of the manuscript.

PREVIOUS PRESENTATION

Abstracts from this project have been submitted as poster presentations at the Annual European Congress of Rheumatology 2018 and the American College of Rheumatology Annual Meeting 2018. The respective abstract references are as follows:

- Ann Rheum Dis, volume 77, supplement Suppl, year 2018, page A639

For Peer Review Only

- Fitzgerald G, Wyse J, Anachebe T, Mullan R, Kane D, McCarroll K, O' Shea F. Lateral DXA More Effective in Detecting Osteoporosis Than Conventional DXA in Axial Spondyloarthropathy [abstract]. Arthritis Rheumatol. 2018; 70 (suppl 10). https://acrabstracts.org/abstract/lateral-dxa-more-effective-in-detecting-osteoporosis-than-conventional-dxa-in-axial-spondyloarthropathy/. Accessed January 25, 2019.

GF was additionally awarded the William Stokes Award from the Royal College of Physicians of Ireland for this research.

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REFERENCES

1. Molto A, Etcheto A, van der Heijde D, Landewe R, van den Bosch F, Bautista Molano W, et al. Prevalence of comorbidities and evaluation of their screening in spondyloarthritis: results of the international cross-sectional ASAS-COMOSPA study. Ann Rheum Dis. 2016;75:1016-23.

2. Akgol G, Kamanli A, Ozgocmen S. Evidence for inflammation-induced bone loss in non-radiographic axial spondyloarthritis. Rheumatology (Oxford). 2014;53:497-501.

3. Nigil Haroon N, Szabo E, Raboud JM, McDonald-Blumer H, Fung L, Josse RG, et al. Alterations of bone mineral density, bone microarchitecture and strength in patients with ankylosing spondylitis: a cross-sectional study using high-resolution peripheral quantitative computerized tomography and finite element analysis. Arthritis Res Ther. 2015;17:377.

4. Forien M, Molto A, Etcheto A, Dougados M, Roux C, Briot K. Bone mineral density in patients with symptoms suggestive of spondyloarthritis. Osteoporos Int. 2015;26:1647-53.

5. Ramirez J, Nieto-Gonzalez JC, Curbelo Rodriguez R, Castaneda S, Carmona L. Prevalence and risk factors for osteoporosis and fractures in axial spondyloarthritis: A systematic review and meta-analysis. Semin Arthritis Rheum. 2018;48:44-52.

6. Vosse D, Landewé R, van der Heijde D, van der Linden S, van Staa T-P, Geusens P. Ankylosing spondylitis and the risk of fracture: results from a large primary care-based nested case-control study. Ann Rheum Dis. 2009;68:1839-42.

7. Robinson Y, Sanden B, Olerud C. Increased occurrence of spinal fractures related to ankylosing spondylitis: a prospective 22-year cohort study in 17,764 patients from a national registry in Sweden. Patient Saf Surg. 2013;7:2.

For Peer Review Only

8. Montala N, Juanola X, Collantes E, Munoz-Gomariz E, Gonzalez C, Gratacos J, et al. Prevalence of vertebral fractures by semiautomated morphometry in patients with ankylosing spondylitis. J Rheumatol. 2011;38:893-7.

9. Westerveld LA, Verlaan JJ, Oner FC. Spinal fractures in patients with ankylosing spinal disorders: a systematic review of the literature on treatment, neurological status and complications. Eur Spine J. 2009;18:145-56.

10. Westerveld LA, van Bemmel JC, Dhert WJ, Oner FC, Verlaan JJ. Clinical outcome after traumatic spinal fractures in patients with ankylosing spinal disorders compared with control patients. Spine J. 2014;14:729-40.

11. Geusens P, De Winter L, Quaden D, Vanhoof J, Vosse D, van den Bergh J, et al. The prevalence of vertebral fractures in spondyloarthritis: relation to disease characteristics, bone mineral density, syndesmophytes and history of back pain and trauma. Arthritis Res Ther. 2015;17.

12. Klingberg E, Geijer M, Gothlin J, Mellstrom D, Lorentzon M, Hilme E, et al. Vertebral fractures in ankylosing spondylitis are associated with lower bone mineral density in both central and peripheral skeleton. J Rheumatol. 2012;39:1987-95.

13. Ulu MA, Cevik R, Dilek B. Comparison of PA spine, lateral spine, and femoral BMD measurements to determine bone loss in ankylosing spondylitis. Rheumatol Int. 2013;33:1705-11.

14. Donnelly S, Doyle DV, Denton A, Rolfe I, McCloskey EV, Spector TD. Bone mineral density and vertebral compression fracture rates in ankylosing spondylitis. Ann Rheum Dis. 1994;53:117-21.

For Peer Review Only

15. Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2011;70:896-904.

16. van der Heijde D, Ramiro S, Landewe R, Baraliakos X, Van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017;76:978-91.

17. Black DM, Rosen CJ. Clinical Practice. Postmenopausal Osteoporosis. N Engl J Med. 2016;374:254-62.

18. Haroon N. Ankylosis in ankylosing spondylitis: current concepts. Clin Rheumatol. 2015;34:1003-7.

19. Magrey MN, Khan MA. The Paradox of Bone Formation and Bone Loss in Ankylosing Spondylitis: Evolving New Concepts of Bone Formation and Future Trends in Management. Curr Rheumatol Rep. 2017;19:17.

20. Van Mechelen M, Gulino GR, de Vlam K, Lories R. Bone Disease in Axial Spondyloarthritis. Calcif Tissue Int. 2018;102:547-58.

21. Schousboe JT, Shepherd JA, Bilezikian JP, Baim S. Executive summary of the 2013 International Society for Clinical Densitometry Position Development Conference on bone densitometry. J Clin Densitom. 2013;16:455-66.

22. Carter S, Lories RJ. Osteoporosis: a paradox in ankylosing spondylitis. Current osteoporosis reports. 2011;9:112-5.

23. Finkelstein JS, Cleary RL, Butler JP, Antonelli R, Mitlak BH, Deraska DJ, et al. A comparison of lateral versus anterior-posterior spine dual energy x-ray absorptiometry for the diagnosis of osteopenia. The Journal of Clinical Endocrinology & Metabolism. 1994;78:724-30.

For Peer Review Only

24. Blake GM, Jagathesan T, Herd RJ, Fogelman I. Dual X-ray absorptiometry of the lumbar spine: the precision of paired anteroposterior/lateral studies. Br J Radiol. 1994;67:624-30.

25. Malochet-Guinamand S, Pereira B, Tatar Z, Tournadre A, Molto A, Dougados M, et al. Prevalence and risk factors of low bone mineral density in spondyloarthritis and prevalence of vertebral fractures. BMC Musculoskelet Disord. 2017;18:357.

26. Deminger A, Klingberg E, Lorentzon M, Geijer M, Gothlin J, Hedberg M, et al. Which measuring site in ankylosing spondylitis is best to detect bone loss and what predicts the decline: results from a 5-year prospective study. Arthritis Res Ther. 2017;19:273.

27. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol. 1994;21:1694-8.

28. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol. 1994;21:2286-91.

29. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol. 1994;21:2281-5.

30. Doward LC, Spoorenberg A, Cook SA, Whalley D, Helliwell PS, Kay LJ, et al. Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis. 2003;62:20-6.

31. Jones SD, Steiner A, Garrett SL, Calin A. The Bath Ankylosing Spondylitis Patient Global Score (BAS-G). Br J Rheumatol. 1996;35:66-71.

For Peer Review Only

32. Pincus T, Summey JA, Soraci SA, Jr., Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. Arthritis Rheum. 1983;26:1346-53.

33. Lukas C, Landewe R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis. 2009;68:18-24.

34. Creemers MC, Franssen MJ, van't Hof MA, Gribnau FW, van de Putte LB, van Riel PL. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis. 2005;64:127-9.

35. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984;27:361-8.

36. Shepherd JA, Schousboe JT, Broy SB, Engelke K, Leslie WD. Executive Summary of the 2015 ISCD Position Development Conference on Advanced Measures From DXA and QCT: Fracture Prediction Beyond BMD. J Clin Densitom. 2015;18:274-86.

37. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med. 1993;94:646-50.

38. Fitzgerald GE, O'Shea FD. The Fascinating Paradox of Osteoporosis in Axial Spondyloarthropathy. The Journal of rheumatology. 2017;44:1767-76.

39. Klingberg E, Lorentzon M, Mellstrom D, Geijer M, Gothlin J, Hilme E, et al. Osteoporosis in ankylosing spondylitis - prevalence, risk factors and methods of assessment. Arthritis Res Ther. 2012;14:R108.

40. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet. 2002;359:1929-36.

For Peer Review Only

41. Qu X, Huang X, Jin F, Wang H, Hao Y, Tang T, et al. Bone mineral density and all-cause, cardiovascular and stroke mortality: a meta-analysis of prospective cohort studies. Int J Cardiol. 2013;166:385-93.

42. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organ Tech Rep Ser. 1994;843:1-129.

43. Zmuda JM, Cauley JA, Glynn NW, Finkelstein JS. Posterior-anterior and lateral dual-energy x-ray absorptiometry for the assessment of vertebral osteoporosis and bone loss among older men. J Bone Miner Res. 2000;15:1417-24.

44. Rajamanohara R, Robinson J, Rymer J, Patel R, Fogelman I, Blake GM. The effect of weight and weight change on the long-term precision of spine and hip DXA measurements. Osteoporos Int. 2011;22:1503-12.

45. Patel R, Blake GM, Rymer J, Fogelman I. Long-term precision of DXA scanning assessed over seven years in forty postmenopausal women. Osteoporos Int. 2000;11:68-75.

46. Karberg K, Zochling J, Sieper J, Felsenberg D, Braun J. Bone loss is detected more frequently in patients with ankylosing spondylitis with syndesmophytes. J Rheumatol. 2005;32:1290-8.

47. Toussirot E, Michel F, Wendling D. Bone density, ultrasound measurements and body composition in early ankylosing spondylitis. Rheumatology (Oxford). 2001;40:882-8.

48. Sarikaya S, Basaran A, Tekin Y, Ozdolap S, Ortancil O. Is osteoporosis generalized or localized to central skeleton in ankylosing spondylitis? J Clin Rheumatol. 2007;13:20-4.

49. Pray C, Feroz NI, Nigil Haroon N. Bone Mineral Density and Fracture Risk in Ankylosing Spondylitis: A Meta-Analysis. Calcif Tissue Int. 2017;101:182-92.

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Table 1: Baseline demographic and clinical characteristics of the axSpA cohort

Variable	Whole population (n=100)
Males; n (%)	78 (78)
Age, years; mean (SD)	51.6 (11.6)
Caucasian; n (%)	98 (98)
Disease duration, years; mean (SD)	25.7 (12.9)
Delay to diagnosis, years; mean (SD)	8.9 (8.6)
Employment status; n (%)	
Employed	54 (54)
Disability due to axSpA	15 (15)
Smoking status; n (%)	
Current	25 (25)
Past	47 (47)
Never	28 (28)
Postmenopausal women; n (%§)	13 (59)
HLA-B27 positive*; n (%)	83 (84.7)
BMI, kg/m²; mean (SD)	28.1 (5.5)
Modified New York criteria; n (%)	85 (85)
Extra-articular manifestations; n (%)	
Uveitis	29 (29)
Psoriasis	16 (16)
IBD	16 (16)
Treatment; n (%)	

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NSAIDs	43 (43)
Steroids use >3 months	14 (14)
Biologic exposure	70 (70)
Calcium supplement	17 (17)
Vitamin D supplement	26 (26)
Disease severity; median (25th, 75th percentile)	
ASDAS-CRP	2.2 (1.6, 3.0)
ASDAS-ESR	2.0 (1.3, 2.9)
BASDAI	3.9 (2.1, 5.6)
BASFI	4.0 (1.4, 5.7)
BASMI	4.2 (2.8, 6)
HAQ	0.63 (0.13, 1.00)
ASQoL	6 (2, 11)
mSASSS	10 (4, 37.3)
Bloods, median (25th, 75th percentile)	
Haemoglobin, g/dL	14.6 (13.4, 15.5)
ESR, mm/h	6 (2, 15)
CRP, g/dL	2.4 (0, 8.1)
Urea	5.0 (4.3, 6.3)
Creatinine	78 (67, 87)
Vitamin D	65 (43, 84)
PTH	40.6 (31.4, 52.3)
Self-reported fragility fracture; n (%)	3 (3)

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Osteoporosis risk factor, any; n (%)	33 (33)
Bone mineral density, g/cm^2; mean (SD)	
PA lumbar spine	1.08 (0.19)
Lateral lumbar spine	0.74 (0.14)
Femoral neck	0.80 (0.11)
Total hip	0.96 (0.12)

*HLA-B27 status unknown in n=2. §Calculated as % of women (n=22) in study. ASQoL: Ankylosing Spondylitis Quality of Life; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath AS Disease Activity Index; BASFI; Bath AS Functional Index; BASMI: Bath AS Metrology Index; BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HAQ: Health assessment questionnaire; HLA: Human leucocyte antigen; IBD: inflammatory bowel disease; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; NSAIDS: non-steroidal anti-inflammatory drugs; PA: postero-anterior; PTH: parathyroid hormone.

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Table 2: Correlation between variables and (a) each measured BMD site (b) difference between PA and lateral BMD.

(a)	Lateral spine BMD§	FN BMD§	TH BMD§	Age§	BMI§	mSASSS†	BASMI§
PA spine BMD	0.55**	0.48**	0.52**	0.23*	0.43**	0.41**	0.48**
Lateral spine BMD	…	0.43**	0.55**	-0.12	0.21*	0.07	0.02
FN BMD	…	…	0.82**	-0.19	0.18	0.00	0.02
TH BMD	…	…	…	-0.15	0.34**	-0.03	-0.06
Age	…	…	…	…	0.13	0.55**	0.58
BMI	…	…	…	…	…	0.28**	0.30**
mSASSS	…	…	…	…	…	…	0.77**

(b)	Age§	BASDAI§	BASMI§	mSASSS†	BASFI§	CRP§	BMI§
PA – lateral BMD	0.38**	0.01	0.54**	0.51**	0.32**	0.03	0.32**

§ Correlation coefficient is Pearson's r; †Correlation coefficient is Spearman correlation coefficient, rho; ** p<0.01; * p<0.05; … denotes duplicate cell, left blank for clarity of presentation; BASDAI: Bath AS disease activity index; BASFI: Bath AS functional index; BASMI: Bath AS metrology index; BMD: bone mineral density; BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FN: femoral neck; mSASSS: modified Stokes Ankylosing Spondylitis Score; PA: posteroanterior; TH: total hip.

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Table 3: Multiple regression model, variables associated with difference between PA and lateral BMD of the spine.

Variable	ß	95% CI	P Value
Gender[a]	-0.028	-0.093 to 0.037	0.40
Disease duration	0.003	0.001 to 0.005	**0.01**
Biologic exposure[b]	0.015	-0.043 to 0.072	0.60
BMI	0.009	0.003 to 0.014	**<0.01**
mSASSS	0.002	0.001 to 0.004	**<0.01**

a: reference group (0) is male; b: reference group (0) is no biologic exposure; BMI: body mass index; CI: confidence interval; mSASSS: modified Stokes Ankylosing Spondylitis Spinal Score.

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Supplementary table 1: Difference in BMD at each measured site for a selection of variables.

Variable	Bone mineral density (BMD), g/cm^2			
	PA spine	Lateral spine	Femoral neck	Total hip
Male	1.11	0.76	0.81	0.98
Female	0.98	0.67	0.75	0.90
P value	***<0.001***	***0.01***	***0.01***	***0.01***
Smoker	1.07	0.74	0.11	0.12
Non-smoker	1.11	0.74	0.11	0.11
P value	*0.40*	*0.97*	*0.71*	*0.99*
Biologic exposure	1.08	0.74	0.80	0.96
No biologic exposure	1.09	0.76	0.79	0.96
P value	*0.74*	*0.52*	*0.77*	*0.98*
HLA-B27 positive	1.08	0.74	0.80	0.96
HLA-B27 negative	1.10	0.76	0.81	0.98
P value	*0.72*	*0.66*	*0.63*	*0.54*
Osteoporosis risk factor*	1.11	0.75	0.78	0.94
No osteoporosis risk factor	1.07	0.74	0.81	0.97
P value	*0.36*	*0.63*	*0.17*	*0.32*

*At least one of: parental hip fracture, steroid use > 3 months, daily alcohol > 2 units, type 1 diabetes mellitus, osteogenesis imperfecta, uncontrolled hyperthyroidism, early menopause, hypogonadism, malabsorption, chronic liver disease, eating disorder, Cushing's

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disease, transplant, hyperparathyroidism, end-stage kidney disease. HLA: human leucocyte antigen.

Figure 1: Scatter plot demonstrating difference between PA and lateral DXA projections of the spine, stratified by gender; DXA: dual-energy x-ray absorptiometry; PA: posteroanterior.

Figure 2: Prevalence of normal BMD, osteopenia and osteoporosis at each measured site, in men ≥ 50 years and post-menopausal women (n=57); BMD: bone mineral density; PA: posteroanterior.

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mSASSS	10 (4, 37.3)
Bloods, median (25th, 75th percentile)	
Haemoglobin, g/dL	14.6 (13.4, 15.5)
ESR, mm/h	6 (2, 15)
CRP, g/	2.4 (0, 8.1)
Urea	5.0 (4.3, 6.3)
Creatinine	78 (67, 87)
Vitamin D	65 (43, 84)
PTH	40.6 (31.4, 52.3)
Self-reported fragility fracture; n (%)	3 (3)

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Osteoporosis risk factor, any; n (%)	33 (33)
Bone mineral density, g/cm^2; mean (SD)	
PA lumbar spine	1.08 (0.19)
Lateral lumbar spine	0.74 (0.14)
Femoral neck	0.80 (0.11)
Total hip	0.96 (0.12)

*HLA-B27 status unknown in n=2. §Calculated as % of women (n=22) in study. ASQoL: Ankylosing Spondylitis Quality of Life; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath AS Disease Activity Index; BASFI; Bath AS Functional Index; BASMI: Bath AS Metrology Index; BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HAQ: Health assessment questionnaire; HLA: Human leucocyte antigen; IBD: inflammatory bowel disease; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; NSAIDS: non-steroidal anti-inflammatory drugs; PA: postero-anterior; PTH: parathyroid hormone.

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Table 2: Correlation between variables and (a) each measured BMD site (b) difference between PA and lateral BMD.

(a)	Lateral spine BMD§	FN BMD§	TH BMD§	Age§	BMI§	mSASSS†	BASMI§
PA spine BMD	0.55**	0.48**	0.52**	0.23*	0.43**	0.41**	0.48**
Lateral spine BMD	…	0.43**	0.55**	-0.12	0.21*	0.07	0.02
FN BMD	…	…	0.82**	-0.19	0.18	0.00	0.02
TH BMD	…	…	…	-0.15	0.34**	-0.03	-0.06
Age	…	…	…	…	0.13	0.55**	0.58
BMI	…	…	…	…	…	0.28**	0.30**
mSASSS	…	…	…	…	…	…	0.77**

(b)	Age§	BASDAI§	BASMI§	mSASSS†	BASFI§	CRP§	BMI§
PA – lateral BMD	0.38**	0.01	0.54**	0.51**	0.32**	0.03	0.32**

§ Correlation coefficient is Pearson's r; †Correlation coefficient is Spearman correlation coefficient, rho; ** p<0.01; * p<0.05; … denotes duplicate cell, left blank for clarity of presentation; BASDAI: Bath AS disease activity index; BASFI: Bath AS functional index; BASMI: Bath AS metrology index; BMD: bone mineral density; BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FN: femoral neck; mSASSS: modified Stokes Ankylosing Spondylitis Score; PA: posteroanterior; TH: total hip.

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Table 3: Multiple regression model, variables associated with difference between PA and lateral BMD of the spine.

Variable	ß	95% CI	P Value
Gender[a]	-0.028	-0.093 to 0.037	0.40
Disease duration	0.003	0.001 to 0.005	**0.01**
Biologic exposure[b]	0.015	-0.043 to 0.072	0.60
BMI	0.009	0.003 to 0.014	**<0.01**
mSASSS	0.002	0.001 to 0.004	**<0.01**

a: reference group (0) is male; b: reference group (0) is no biologic exposure; BMI: body mass index; CI: confidence interval; mSASSS: modified Stokes Ankylosing Spondylitis Spinal Score.

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Supplementary table 1: Difference in BMD at each measured site for a selection of variables.

Variable	Bone mineral density (BMD), g/cm^2			
	PA spine	Lateral spine	Femoral neck	Total hip
Male	1.11	0.76	0.81	0.98
Female	0.98	0.67	0.75	0.90
P value	***<0.001***	***0.01***	***0.01***	***0.01***
Smoker	1.07	0.74	0.11	0.12
Non-smoker	1.11	0.74	0.11	0.11
P value	*0.40*	*0.97*	*0.71*	*0.99*
Biologic exposure	1.08	0.74	0.80	0.96
No biologic exposure	1.09	0.76	0.79	0.96
P value	*0.74*	*0.52*	*0.77*	*0.98*
HLA-B27 positive	1.08	0.74	0.80	0.96
HLA-B27 negative	1.10	0.76	0.81	0.98
P value	*0.72*	*0.66*	*0.63*	*0.54*
Osteoporosis risk factor*	1.11	0.75	0.78	0.94
No osteoporosis risk factor	1.07	0.74	0.81	0.97

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P value	*0.36*	*0.63*	*0.17*	*0.32*

*At least one of: parental hip fracture, steroid use > 3 months, daily alcohol > 2 units, type 1 diabetes mellitus, osteogenesis imperfecta, uncontrolled hyperthyroidism, early menopause, hypogonadism, malabsorption, chronic liver disease, eating disorder, Cushing's disease, transplant, hyperparathyroidism, end-stage kidney disease. HLA: human leucocyte antigen.

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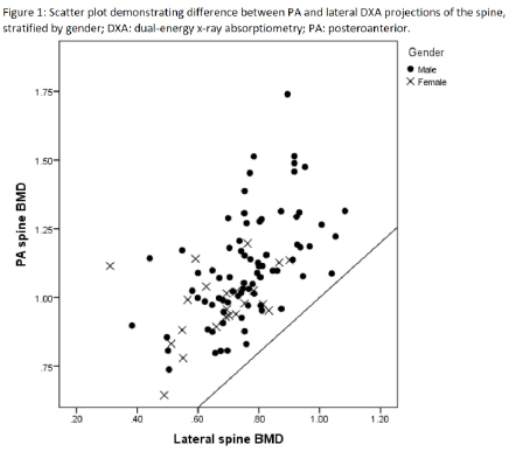

Figure 1: Scatter plot demonstrating difference between PA and lateral DXA projections of the spine, stratified by gender; DXA: dual-energy x-ray absorptiometry; PA: posteroanterior.

Scatter plot demonstrating difference between PA and lateral DXA projections of the spine, stratified by gender; DXA: dual-energy x-ray absorptiometry; PA: posteroanterior.

203x131mm (240 x 240 DPI)

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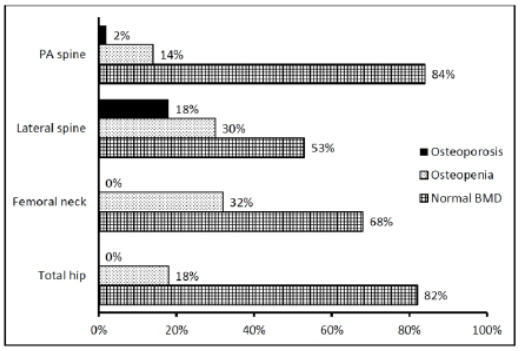
Figure 2: Prevalence of normal BMD, osteopenia and osteoporosis at each measured site, in men ≥ 50 years and post-menopausal women (n=57); BMD: bone mineral density; PA: posteroanterior.



Prevalence of normal BMD, osteopenia and osteoporosis at each measured site, in men ≥ 50 years and post-menopausal women (n=57); BMD: bone mineral density; PA: posteroanterior.

203x114mm (240 x 240 DPI)

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ABSTRACT NUMBER: 1620

Lateral DXA More Effective in Detecting Osteoporosis Than Conventional DXA in Axial Spondyloarthropathy

Gillian Fitzgerald[1,2], Jason Wyse[3], Tochukwu Anachebe[4], Ronan Mullan[5], David Kane[6], Kevin McCarroll[7] and Finbar O' Shea[2], [1]School of Medicine, Trinity College Dublin, Dublin 2, Ireland, [2]Rheumatology, St. James's Hospital, Dublin 8, Ireland, [3]School of Computer Science and Statistics, Trinity College Dublin, Dublin 2, Ireland, [4]Department of Rheumatology, St. James's Hospital, Dublin 8, Ireland, [5]Department of Rheumatology,, Tallaght Hospital, Dublin, Ireland, [6]Department of Rheumatology, Tallaght Hospital, TCD, Dublin 24, Ireland, [7]Department of Medicine for the Elderly, St. James's Hospital, Dublin 8, Ireland

Meeting: 2018 ACR/ARHP Annual Meeting

Keywords: axial spondyloarthritis, Bone density, diagnosis and dual energy x-ray absorptiometry (DEXA)

SESSION INFORMATION

Date: Monday, October 22, 2018

Session Type: ACR Poster Session B

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Time: 9:00AM-11:00AM

Background/Purpose:

The severe consequences of osteoporosis in the general population are well outlined. In axial spondyloarthropathy (axSpA), osteoproliferation of the spine means posterioanterior (PA) dual-energy x-ray absorptiometry (DXA) can't discriminate between new bone formation and vertebral body, potentially overestimating BMD. To understand the impact of low BMD in axSpA, we need an accurate and reproducible method of assessment. Lateral DXA of the spine avoids spinal osteoproliferation and is an attractive option. The aim of this study is to compare lateral DXA of the lumbar spine with PA DXA, and determine patient variables that render conventional DXA unreliable.

Methods:

Patients fulfilling modified New York (mNY) or Assessment of Spondyloarthritis International Society (ASAS) criteria were consecutively recruited from rheumatology clinics in this twin-centre cross-sectional study. A detailed assessment of patients included demographics, clinical exam, laboratory assessment and validated measures of disease severity (BASDAI, ASDAS-CRP, BASMI, mSASSS). BMD of the spine was assessed using DXA in the lateral and PA projections. BMD of the hip was assessed in the conventional manner. R software was used for statistical analysis.

Results:

One hundred and ten patients were assessed, 100 of whom had paired AP and lateral DXAs: 76% (n=84) male, 92% Caucasian, 81% mNY criteria. Median (IQR) age was 52 (17) years, disease duration 23.5 (20) years, delay to diagnosis 7 (12) years, body mass index (BMI) 27.6 (6.3) kg/m^2, BASDAI 3.9 (2.1-5.6), BASMI 4.1 (2.8-5.8), ASDAS-CRP 2.2 (1.5-3), mSASSS 8.5 (2-36).

ABSTRACT NUMBER: 675

Quantitative Ultrasound of the Calcaneus Has a Role to Play in Detecting Low Bone Mineral Density in Axial Spondyloarthropathy Patients

Gillian Fitzgerald[1,2], Tochukwu Anachebe[3], Ronan Mullan[4], David Kane[5], Kevin McCarroll[6] and Finbar O' Shea[2], [1]School of Medicine, Trinity College Dublin, Dublin 2, Ireland, [2]Rheumatology, St. James's Hospital, Dublin 8, Ireland, [3]Department of Rheumatology, St. James's Hospital, Dublin 8, Ireland, [4]Department of Rheumatology,, Tallaght Hospital, Dublin, Ireland, [5]Department of Rheumatology, Tallaght Hospital, Dublin 24, Ireland, [6]Department of Medicine for the Elderly, St. James's Hospital, Dublin 8, Ireland

Meeting: 2018 ACR/ARHP Annual Meeting

Keywords: axial spondyloarthritis, Bone density, diagnosis, dual energy x-ray absorptiometry (DEXA) and ultrasound

SESSION INFORMATION

Date: Sunday, October 21, 2018

Session Type: ACR Poster Session A

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Time: 9:00AM-11:00AM

Background/Purpose:

Axial spondyloarthropathy (axSpA) patients have an increased risk of developing osteoporosis compared to matched controls. Dual energy x-ray absorptiometry (DXA) is the technique of choice to detect low bone mineral density (BMD). Quantitative ultrasound (QUS) of the calcaneus measures 3 parameters of bone: speed of sound (SOS), broadband ultrasound attenuation (BUA) and stiffness index (SI; composite of SOS and BUA) and can predict fragility fractures in postmenopausal women. QUS is cheap, portable and does not use any ionising radiation. It also provides information on bone microarchitecture, as well as bone mineral density (BMD). Few studies have investigated the use of QUS in axSpA. We aimed to investigate relationships between DXA and QUS in a well characterised axSpA cohort.

Methods:

Patients fulfilling modified New York (mNY) or Assessment of Spondyloarthritis International Society (ASAS) criteria were consecutively recruited from rheumatology clinics in this twin-centre cross-sectional study. DXA assessed BMD at the spine, hip and radius. QUS of the calcaneus generated SOS, BUA and SI. Patients had a detailed assessment that included demographics, clinical exam, laboratory assessment and validated measures of disease severity (BASDAI, ASDAS-CRP, BASMI, mSASSS) collected. SPSS was used for statistical analysis.

Results:

A total of 107 patients were included: 76% male, 81% mNY criteria, median (IQR) age 51.5 (17.8) years, disease duration 23.5 (20.4) years, BASDAI 3.9 (3.6), ASDAS-CRP 2.1 (1.5) and BASMI 4.1 (3.2). Fragility fracture prevalence was low (6%).

ABSTRACT NUMBER: 1621

Higher Serum Uric Acid Levels Protect Against Osteoporosis in Patients with Axial Spondyloarthropathy

Gillian Fitzgerald[1,2], Tochukwu Anachebe[3], Ronan Mullan[4], David Kane[5], Kevin McCarroll[6] and Finbar O' Shea[2], [1]School of Medicine, Trinity College Dublin, Dublin 2, Ireland, [2]Rheumatology, St. James's Hospital, Dublin 8, Ireland, [3]Department of Rheumatology, St. James's Hospital, Dublin 8, Ireland, [4]Department of Rheumatology,, Tallaght Hospital, Dublin, Ireland, [5]Department of Rheumatology, Tallaght Hospital, Dublin 24, Ireland, [6]Department of Medicine for the Elderly, St. James's Hospital, Dublin 8, Ireland

Meeting: 2018 ACR/ARHP Annual Meeting

Keywords: axial spondyloarthritis, Bone density and uric acid

SESSION INFORMATION

Date: Monday, October 22, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster II: Clinical/Epidemiology Studies

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

High serum urate (SUA) is a risk factor for metabolic disease, including hypertension and coronary artery disease. However, SUA has an antioxidant effect and can play a role in protecting against diseases characterised by high oxidative stress, such as neurodegenerative disease. Osteoporosis, a condition defined by bone loss and fragility fractures, is also characterised by high oxidative stress levels, mediated through increased osteoclastic activity. Therefore, antioxidants are of considerable interest due to theoretical protective properties against bone loss. Existing literature examining SUA and its impact on bone mineral density (BMD), particularly in axial spondyloarthropathy (axSpA), is limited. The aim of this study is to examine the relationship between SUA and BMD in a well-characterised axSpA cohort.

Methods:

Patients fulfilling modified New York (mNY) or Assessment of SpondyloArthritis International Society (ASAS) criteria were consecutively recruited from 2 centres in this cross-sectional study. Patients underwent a detailed assessment: demographics, disease-related variables (validated measures of disease activity included BASDAI, ASDAS-CRP, BASMI), clinical examination, laboratory parameters (routine bloods, SUA, CRP, vitamin D). BMD was assessed using dual-energy x-ray absorptiometry of the lumbar spine and hip (total hip and femoral neck). SUA >360 µmol/L (>6 mg/dL) was considered high. Analysis was performed using SPSS.

Results:

A total of 107 patients were included: 76% male, 81% fulfilling mNY criteria, median (IQR) age 51.5 (17.8) years, disease duration 23.5 (20.4) years. Median BMI was 27.6 (6.5) kg/m^2, with 31% of the cohort obese. The median (interquartile range [IQR]) BASDAI was 3.9 (3.6), ASDAS-CRP 2.1 (1.5) and BASMI 4.1 (3.2). Low BMD was present in 38.5% of the cohort and 44% had a previous fracture.

P126

SYNDESMOPHYTES PREVENT ACCURATE DXA ASSESSMENT OF THE SPINE IN AXIAL SPONDYLOARTHROPATHY

Fitzgerald G.E.[1], Anachebe T.[1], McCarroll K.[2], O' Shea F.[1]
[1]Rheumatology Dept., St. James's Hospital; [2]Gerontology Dept., St. James's Hospital, Dublin, Ireland

Background. Axial spondyloarthropathy (axSpA) causes syndesmophytes and ankylosis of the spine.
Osteoporosis is therefore difficult to diagnose, as traditional dual-energy x-ray absorptiometry (DXA) in the antero-posterior (AP) projection of the spine can overestimate bone mineral density (BMD) due to syndesmophytes. Lateral DXA of the lumbar spine is unaffected by syndesmophyte formation.
Aims. 1. Investigate different projections of DXA of the lumbar spine
2. Assess effect of syndesmophytes on spine BMD.
Material/Methods. AxSpA patients were assessed with clinical exam, questionnaires and laboratory investigations. The burden of syndesmophytes was scored using mSASSS, which ranges from 0-72. DXA was performed of the spine in both the AP and lateral projections.
Results. One hundred patients with axSpA were recruited: 78% (n=78) male, mean (SD) age 52 (12) years, disease duration 26 (13) years, median (IQR) mSASSS 10 (33).
Spine BMD was lower by lateral DXA than AP (0.76 vs 1.11 g/cm^2, p<0.01). Lateral DXA detected more cases of low BMD than AP (21% vs 44%, p<0.01). Lateral spine BMD reduced with longer disease (r=-0.3, p=0.02), whereas AP spine BMD increased with age (r=0.3, p=0.01). More women had osteoporosis at the spine than men when measured by lateral DXA (32% vs 12%, p=0.02), but not by AP DXA.
A higher mSASSS, reflecting more syndesmophytes, was associated with a rising AP spine BMD (r=0.5, p<0.01), but had no effect on lateral spine BMD. The gap between AP and lateral spine BMD, i.e. when AP BMD was higher than lateral BMD, increased significantly (p<0.05) with increasing age (r=0.38), disease duration (r=0.37) and mSASSS (r=0.52). mSASSS was the strongest predictor of a difference between AP and lateral BMD measurements, suggesting syndesmophyte formation interferes with AP DXA of the spine.
Conclusion. AP DXA of the spine is affected by a higher burden of syndesmophytes, raising concerns traditional DXA may miss cases of osteoporosis. We suggest lateral DXA of the spine may be more accurate in axSpA patients.

P125

OSTEOPOROSIS COMMONLY OCCURS IN AXIAL SPONDYLOARTHROPATHY

Fitzgerald G.E.[1], Anachebe T.[1], McCarroll K.[2], O' Shea F.[1]
[1]Rheumatology Dept., St. James's Hospital; [2]Gerontology Dept., St. James's Hospital, Dublin, Ireland

Background. Osteoporosis, a consequence of inflammatory arthritis, is frequently overlooked in axSpA, a condition with male predominance. Osteoporosis prevalence figures are therefore uncertain. To understand the impact of low BMD in axSpA, accurate epidemiology is crucial.
Aims. 1. Investigate the prevalence of low BMD in an axSpA cohort
2. Explore relationships between BMD and axSpA.
Materials and Methods. A detailed assessment was performed on axSpA patients. Disease severity was assessed using ASDAS-CRP, BASDAI, BASMI and BASFI. BMD was assessed using DXA of the spine, hip and radius. The WHO criteria were used to classify low BMD.
Results. One hundred and four patients with axSpA were consecutively recruited: 77.9% (n=81) male, 98.1% (n=102) Caucasian, mean (SD) age 51 (12) years, disease duration 26 (13) years. The mean (SD) ASDAS-CRP was 2.3 (1), BASDAI was 3.9 (2.2), BASMI was 4.3 (1.9) and BASFI was 3.8 (2.5). Prior fracture was present in 42.3% (n=44) of patients, with 3 fragility fractures.
Of the cohort, 42.3% (n=44) had osteopenia and 16.3% (n=17) had osteoporosis. Low BMD was most prevalent at the spine, with 44% of the cohort affected, followed by the femoral neck (30.1%, n=22). Low BMD at the radius was uncommon (<10% of the cohort). Only 6.4% of the cohort had a prior diagnosis of osteoporosis and only 39.4% had a previous DXA.
Female gender, higher BASFI, lower BMI and lower urate levels were significantly associated with bone loss at spine and hip. ASDAS-CRP and BASDAI had no impact on BMD. Longer disease duration was associated with spine BMD loss. Non-obese patients were more likely to have low BMD than obese patients (62.3% vs 40%, OR 2.5, p=0.04). Biologics use didn't influence BMD.
Conclusion. Low BMD is common in axSpA, with over 50% affected. Most cases of low BMD were undiagnosed prior to this study. Less than half of the cohort had a prior DXA, suggesting continued low awareness of the risk of osteoporosis in axSpA.

FRIDAY, 15 JUNE 2018
Spondyloarthritis – clinical aspects (other than treatment)

FRI0196 Traditional dxa underestimates bone mineral density of the spine in axial spondyloarthropathy FREE

G. Fitzgerald, T. Anachebe, F. O' Shea

Author affiliations +

Abstract

Background Axial spondyloarthropathy (axSpA) is an inflammatory arthritis which can lead to new bone formation (syndesmophytes) and ankylosis of the spine. Osteoporosis is a recognised feature of axSpA, but can be challenging to diagnose. Traditional dual-energy x-ray absorptiometry (DXA) in the antero-posterior (AP) projection of the spine can overestimate bone mineral density (BMD) due to the presence of syndesmophytes, potentially under-diagnosing osteoporosis. There is a real need to find an accurate method to assess BMD in axSpA patients. Lateral DXA of the lumbar spine is unaffected by syndesmophyte formation and may be a promising tool.

Objectives The aim of this study is to:

1. investigate different projections of DXA of the lumbar spine in axSpA patients

2. assess the effect of syndesmophytes on spine BMD.

Methods AxSpA patients were assessed with clinical exam, questionnaires and laboratory investigations. The burden of syndesmophytes on lateral x-rays of the lumbar and cervical spine was assessed with the validated modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) score, which ranges from 0–72 (higher scores indicate more severe disease). DXA was performed of the spine in both the AP and lateral projections. SPSS was used for statistical analysis.

Results One hundred patients with axSpA were recruited: 78% (n=78) male, mean (SD) age 52 [12] years, disease duration 26 [13] years, 85% (n=85) fulfil modified New York criteria. The median (IQR) mSASSS score was 10. [33]

Lumbar spine BMD was lower when measured by lateral DXA rather than AP (0.76 v 1.11 g/cm^2, p<0.01). Lateral DXA detected more cases of spinal osteopenia or osteoporosis than AP (21% v 44%, p<0.01). Lateral spine BMD reduced with longer duration of disease (r=-0.3, p=0.02), whereas AP spine BMD increased with age (r=0.3, p=0.01). Women had significantly more cases of osteoporosis at the lumbar spine than men when measured by lateral DXA (32% v 12%, p=0.02), but not by AP DXA.

A higher mSASSS, reflecting more syndesmophytes/new bone formation, was associated with a rising AP spine BMD (r=0.5, p<0.01), but had no effect on lateral spine BMD. The gap between AP and lateral spine BMD, i.e. when AP BMD was higher than lateral BMD, increased significantly (p<0.05) with increasing age (r=0.38), disease duration (r=0.37) and mSASSS (r=0.52). mSASSS was the strongest independent predictor of a difference between AP and lateral BMD measurements, suggesting that syndesmophyte formation interferes with AP DXA assessment of the spine.

Conclusions AP DXA of the spine is affected by a higher burden of syndesmophytes (new bone formation), raising concerns that traditional DXA assessment may miss cases of osteoporosis. We suggest that lateral DXA of the spine may be a more accurate tool to detect osteoporosis in axSpA patients.

ABSTRACT NUMBER: 675

Quantitative Ultrasound of the Calcaneus Has a Role to Play in Detecting Low Bone Mineral Density in Axial Spondyloarthropathy Patients

Gillian Fitzgerald[1,2], Tochukwu Anachebe[3], Ronan Mullan[4], David Kane[5], Kevin McCarroll[6] and Finbar O' Shea[2], [1]School of Medicine, Trinity College Dublin, Dublin 2, Ireland, [2]Rheumatology, St. James's Hospital, Dublin 8, Ireland, [3]Department of Rheumatology, St. James's Hospital, Dublin 8, Ireland, [4]Department of Rheumatology,, Tallaght Hospital, Dublin, Ireland, [5]Department of Rheumatology, Tallaght Hospital, Dublin 24, Ireland, [6]Department of Medicine for the Elderly, St. James's Hospital, Dublin 8, Ireland

Meeting: 2018 ACR/ARHP Annual Meeting

Keywords: axial spondyloarthritis, Bone density, diagnosis, dual energy x-ray absorptiometry (DEXA) and ultrasound

SESSION INFORMATION

Date: Sunday, October 21, 2018

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Imaging, Clinical Studies, and Treatment

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Axial spondyloarthropathy (axSpA) patients have an increased risk of developing osteoporosis compared to matched controls. Dual energy x-ray absorptiometry (DXA) is the technique of choice to detect low bone mineral density (BMD). Quantitative ultrasound (QUS) of the calcaneus measures 3 parameters of bone: speed of sound (SOS), broadband ultrasound attenuation (BUA) and stiffness index (SI; composite of SOS and BUA) and can predict fragility fractures in postmenopausal women. QUS is cheap, portable and does not use any ionising radiation. It also provides information on bone microarchitecture, as well as bone mineral density (BMD). Few studies have investigated the use of QUS in axSpA. We aimed to investigate relationships between DXA and QUS in a well characterised axSpA cohort.

Methods:

Patients fulfilling modified New York (mNY) or Assessment of Spondyloarthritis International Society (ASAS) criteria were consecutively recruited from rheumatology clinics in this twin-centre cross-sectional study. DXA assessed BMD at the spine, hip and radius. QUS of the calcaneus generated SOS, BUA and SI. Patients had a detailed assessment that included demographics, clinical exam, laboratory assessment and validated measures of disease severity (BASDAI, ASDAS-CRP, BASMI, mSASSS) collected. SPSS was used for statistical analysis.

Results:

A total of 107 patients were included: 76% male, 81% mNY criteria, median (IQR) age 51.5 (17.8) years, disease duration 23.5 (20.4) years, BASDAI 3.9 (3.6), ASDAS-CRP 2.1 (1.5) and BASMI 4.1 (3.2). Fragility fracture prevalence was low (6%).

THU0255 Low bone mineral density is common in axial spondyloarthropathy FREE

G. Fitzgerald, T. Anachebe, F. O' Shea

Author affiliations +

Abstract

Background Osteoporosis is a known consequence of inflammatory arthritis (IA). In the general population and IA such as rheumatoid arthritis, the impact of osteoporosis is well outlined. However, it is often ignored in axial spondyloarthropathy (axSpA), a form of IA centred on sacroiliac joints and the spine, as axSpA predominantly affects men, in whom osteoporosis is often not considered. As a result, osteoporosis prevalence figures are unclear, with wide variation in the literature. Accurate epidemiology regarding bone mineral density (BMD) in axSpA is crucial to begin understanding the impact of low BMD in this cohort.

Objectives 1. Investigate the prevalence of low BMD in a well-characterised axSpA cohort

2. Explore relationships (demographic, disease-related, laboratory) between BMD and axSpA.

Methods A detailed assessment was performed on axSpA patients, including demographics, clinical characteristics and laboratory investigations. Disease severity was assessed with tools validated in axSpA: ASDAS-CRP and BASDAI (disease activity), BASMI (spinal mobility) and BASFI (function). BMD was assessed using DXA of the spine, hip and radius. Lateral vertebral assessment (LVA) was also performed. The WHO criteria were used to classify low BMD. SPSS was used for statistical analysis.

Results One hundred and four patients with axSpA were consecutively recruited: 77.9% (n=81) male, 98.1% (n=102) Caucasian, mean (SD) age 51^{12} years, disease duration 26^{13} years. The mean (SD) ASDAS-CRP was 2.3 (1), BASDAI was 3.9 (2.2), BASMI was 4.3 (1.9) and BASFI was 3.8 (2.5), reflecting mild to moderate disease burden. A history of fracture was present in 42.3% (n=44) of the cohort, with only 3 fragility fractures reported.

Of the cohort, 42.3% (n=44) had osteopenia and 16.3% (n=17) had osteoporosis. Low BMD was most prevalent at the spine, with 44% of the cohort affected, followed by the femoral neck (30.1%, n=22). Low BMD at the radius was uncommon (<10% of the cohort). Only 6.4% of the cohort had a prior diagnosis of osteoporosis and only 39.4% had a previous DXA.

Three vertebral fractures were detected on LVA – all patients were unaware of these fractures prior to the study.

Female gender, higher BASFI, lower BMI and lower urate levels were significantly associated with bone loss at both the spine and the hip. ASDAS-CRP and BASDAI had no impact on low BMD. Additionally, longer disease duration was associated with spine BMD loss. Non-obese patients were more likely to have low BMD at any site than obese patients (62.3% v 40%, OR 2.5, p=0.04). The use of biologics didn't influence BMD.

Conclusions Low BMD is common in this axSpA cohort, with over 50% of patients affected. Most cases of low BMD were undiagnosed prior to this study and less than half of the cohort had ever had a DXA, suggesting a continued low awareness of the risk of osteoporosis in a male-dominated disease.

Appendix B Registered Protocols

B1 Prospero protocol – Study 4 (Systematic review & meta-analysis)

Systematic review

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Interventions, pharmacological and non-pharmacological, for managing bone health in axial

spondyloarthropathy patients: a systematic review and meta-analysis

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

30/07/2018

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

01/03/2019

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.
Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.
This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Gillian Fitzgerald

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Fitzgerald

7. * Named contact email.

Give the electronic mail address of the named contact.

gifitzge@tcd.ie

8. Named contact address

Give the full postal address for the named contact.

Dept of Rheumatology, St. James's Hospital, James's Street, Dublin 8, Ireland

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Trinity College Dublin

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Dr Gillian Fitzgerald. Trinity College Dublin

Ms Megan O' Grady. Trinity College Dublin
Dr Tom O' Dwyer. Trinity College Dublin
Professor Fiona Wilson. Trinity College Dublin
Mr David Mockler. Trinity College Dublin
Dr Finbar O' Shea. St. James's Hospital

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

This project forms part of a PhD project.

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

Yes

GF and BOS have received unrestricted financial support from AbbVie, Pfizer, MSD, UCB, Novartis, Roche and Janssen to attend and/or present at conferences and other educational meetings.

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

What is the optimal intervention for improving bone mineral density in axial spondyloarthropathy?

What is the optimal intervention for preserving bone mineral density in axial spondyloarthropathy?

What effects do pharmacological interventions have on bone mineral density in patients with axial spondyloarthropathy?

What effects do non-pharmacological interventions have on bone mineral density in patients with axial spondyloarthropathy?

What effects do a combination of pharmacological and non-pharmacologcial interventions have on bone mineral density in patients with axial spondyloarthopathy?

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

The following electronic bibliographic databases will be searched: EMBASE, MEDLINE (Ovid), CINAHL, Cochrane Library (central), Web of Science. The search terms will be adapted for use with each bibliographic database.

A hand search of the reference list of eligible studies will also be conducted. There will be no language or date restrictions.

17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy.Do NOT provide links to your search results.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Axial spondyloarthropathy (axSpA) is a chronic inflammatory arthritis, characterised by inflammation of the sacroiliac joints and spine. There is an excess of vertebral fractures in axSpA patients, which are associated with increased morbidity and mortality than vertebral fractures in the general population. Osteoporosis can be defined as "a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture". It is accepted that osteoporosis occurs at an increased frequency in axSpA patients, compared to age- and sex-matched controls.

Pharmacological treatment for osteoporosis has shown efficacy in the general population. Pharmacological treatment for osteoporosis can include calcium and vitamin D supplementation, along with bisphosphonates, parathryoid hormone and denosumab. Non-pharmacological treatment, including exercise interventions, have also shown efficacy in the general population.

To date, the effect of treatment, either pharmacological or non-pharmacological, on bone mineral density has not been explored systematically in axSpA patients.

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion criteria: Adults (male or female aged 18 years or over) diagnosed as having Axial Spondyloarthropathy or Ankylosing Spondylitis according to the 2009 Assessment of SpondyloArthritis Society (ASAS) criteria.

Exclusion criteria: participants under 18 years of age.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Interventions included:

- Any pharmacological therapy specifically prescribed to improve or preserve bone mineral density will be included

- Any non-pharmacological therapy for bone health improvement or preservation will be included

- Any dosage of non-pharmacological prescription, i.e. any frequency, intensity, mode or time will be included.

- Individual or group, supervised or unsupervised, home-based or centre-based studies will be included.

- Combination of pharmacological and non-pharmacological interventions will be included.

- Any pharmacological or non-pharmacological therapy for axSpA will be included, if bone mineral density is measured pre- and post treatment and the other inclusion criteria are satisfied

Excluded:

- General advice to improve bone health without specific pharmacological or non-pharmacological intervention

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Studies comparing intervention group or standard care groups to an intervention group

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion: quasi-randomised or randomised controlled trials in which at least one of the groups received an intervention.

Exclusion:

- observational studies without control groups
- case-control studies
- case reports
- cross-sectional studies
- commentaries
- expert opinion
- review articles.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

This study will examine pharmacological and non-pharmacological interventions delivered in all settings (e.g. hospital-based, primary care, online).

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Bone mineral density at the lumbar spine, femoral neck and total hip measured objectively by any method (e.g. dual-energy x-ray absorptiometry (DXA), quantitative computed tomography (CT)).

Timing and effect measures

Measured at a minimum of two time points

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

None

Timing and effect measures

26. * Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

Two reviewers will independently screen the titles of records returned by the search strategy to identify records that potentially meet the inclusion criteria. Two reviewers will then screen the relevant abstracts to identify studies meeting eligibility criteria. Full-text of potentially relevant reports will be retrieved and assessed for eligibility by two reviewers. Any disagreements on inclusion will be resolved by discussion to achieve consensus and, failing agreement, a third reviewer will be consulted.

A standardised data collection form will be used by two independent researchers to extract relevant data from the included studies. The data extraction form will record variables related to study design, participant characteristics, condition-related factors, pharmacological/non-pharmacological intervention, control group, outcome measures and study results.

27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Two review authors will independently assess potential biases resulting from the trial design. Any discrepancies between review authors will be resolved by discussion to achieve a consensus, with involvement from a third review author where necessary. Risk of bias will be based on the Cochrane collaboration guidelines for assessing risk of bias and will assess the following: - Selection bias - performance / detection bias - attrition bias - reporting bias - other sources of bias.

28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

A narrative synthesis of the findings from the included studies will be presented. Summaries of outcomes, and comparisons with control groups will be conducted for each study by calculating standardised mean differences with 95% confidence intervals for continuous outcomes. If data is suitable (i.e. homogeneous study designs), a meta-analysis will be conducted. If the included studies are not sufficiently homogeneous to combine in a meta-analysis, the results of included studies may still be displayed in a forest plot but without the pooled estimate.

29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

If there are sufficient data, subgroup analysis will be done for patient characteristics (e.g. age, disease duration, ethnicity, gender) and type of intervention (pharmacological versus non-pharmacological), as well

as subset of anatomical region (spine, total hip or femoral neck).

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
Yes

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer

No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
Yes

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Ireland

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

A paper will be submitted to an appropriate high impact journal with the results of this review.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Bone density

Axial spondyloarthropathy

Dual-energy x-ray absorptiometry

Treatment

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published. For newregistrations the review must be Ongoing.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Give the link to the published review.

Appendix C Ethics approval

C1 Study 1 – St. James's Hospital site

C2 Study 1 – Tallaght University Hospital

C3 Studies 2-4

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

Ursula Ryan Ph: 4142342 email: Ursula.Ryan@amnch.ie
Secretariat Fax 4142371

Dr. Barry O'Shea
Rheumatology Department
St. James's Hospital
James Street
Dublin 8

June 19th 2013

Re: Scotland and Ireland Registry for Ankylosing Spondylitis (SIRAS)

REC Reference: 2013/21/06

(Please quote REC reference and EudraCT number on all correspondence)

Dear Dr. O'Shea,

Thank you for your letter dated May 19th 2013, and enclosures in which you request ethical approval of an amendment to the above referenced study.

The Chairman, on behalf of the Research Ethics Committee, has reviewed this proposed amendment on behalf of the Committee and has given ethical approval.

Yours sincerely,

Ms. Ursula Ryan
Secretary
SJH/AMNCH Research Ethics Committee

135703001

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
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TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

SJH/AMNCH Research Ethics Committee
Secretary David Willow, tel: 4142342

Dr Ronan Mullan
Consultant Rheumatologist
Tallaght Hospital.

9th October 2013

Re: Amendment to ASRI registry project. (SIRUS registry)

Ref: 9/10/13/List 37

Dear Dr Mullan

Your correspondence of 30th September refers.
On behalf of the Chair and Committee I can confirm that the proposal to amend the study to recruit patients with ankylosing spondylitis has been noted and approved.

Yours Sincerely

David Willow
Secretary to Research Ethics Committee.

THIS SCREENSHOT MUST NOT BE USED FOR PRESENTATION OR ISSUED TO THIRD PARTIES

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

Dr. Barry O'Shea
Consultant Rheumatologist & General Physician
St. James's Hospital
James's Street
Dublin 8

9th September 2016

Re: Osteoporosis in axial spondyloarthropathy: epidemiology, measurement techniques, risk factors and biomarkers

REC Reference: 2016-08 List 33 (4)
(Please quote reference on all correspondence)

Dear Dr. O'Shea,

Thank you for your correspondence to SJH/AMNCH Research Ethics Committee, in which you requested an amendment in relation to the above referenced study.

The Chairman, Dr. Peter Lavin, on behalf of the Research Ethics Committee, has reviewed this request and grants permission for this amendment.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

The SJH/AMNCH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

Appendix D Outcome measures

D 1 Patient reported outcomes (PRO):

- Pain
- Patient global disease activity
- BAS-G
- BASDAI
- BASFI
- ASQoL

D2 HAQ

D3 BASMI

NAME:_____ DATE:_____ VISIT #: _ _ SITE #: ___ STUDY # : _____

Questionnaire 4: BACK QUESTIONNAIRE

1. PAIN

Please tick the box that represents your answer (☒ 10).

1.1. Nocturnal Back Pain

Based on your assessment, please indicate what is the amount of **back pain at night** that you experienced **during the last week**?

0	1	2	3	4	5	6	7	8	9	10

no pain **most severe pain**

1.2. Total Back Pain

Based on your assessment, please indicate what is the amount of **back pain at any time** that you experienced **during the last week**?

0	1	2	3	4	5	6	7	8	9	10

no pain **most severe pain**

2. PATIENT GLOBAL DISEASE ACTIVITY

2.1. Tick a box to indicate your overall assessment of your disease activity **during the last week?**

0	1	2	3	4	5	6	7	8	9	10

none **severe**

3. BAS - G

3.1. Tick a box to indicate the effect your disease has had on your well-being over **the last week**?

0	1	2	3	4	5	6	7	8	9	10

none **very severe**

3.2. Please indicate the effect your disease has had on your well-being over the **last six months**.

0	1	2	3	4	5	6	7	8	9	10

none **very severe**

4. BASDAI

Please tick the box that represents your answer. (10).
All questions refer to the **last week**.

4.1. How would you describe the overall level of fatigue / tiredness you have experienced?

none **very severe**

4.2. How would you describe the overall level of AS **neck, back or hip** pain you have had?

none **very severe**

4.3. How would you describe the overall level of pain / swelling in joints **other than** neck, back or hips you have had?

none **very severe**

4.4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?

none **very severe**

4.5. How would you describe the overall level of morning stiffness you have had from the time you wake up?

none **very severe**

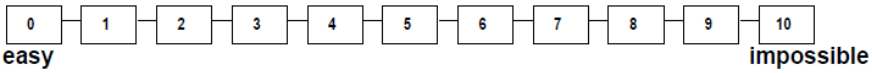
4.6. How long does your morning stiffness last from the time you wake up?

0 hr **1 hr** **2 or more hrs**

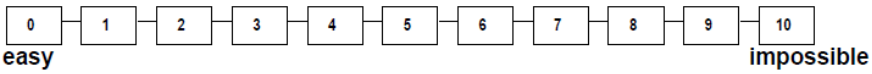
5. BASFI

Please indicate your level of ability with each of the following activities during the last week. 10). An aid is a piece of equipment which helps you to perform an action or movement.

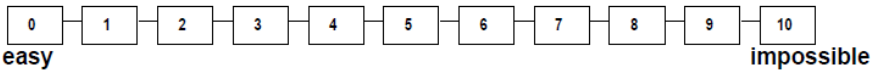
5.1. Putting on your socks or tights without help or aids (e.g. sock aid).



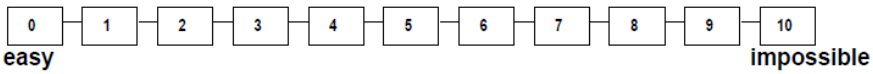
5.2. Bending forward from the waist to pick up a pen from the floor without an aid.



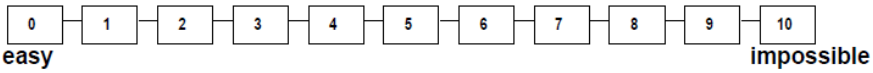
5.3. Reaching up to a high shelf without help or aids (e.g. helping hand).



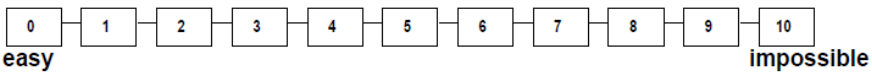
5.4. Getting up out of an armless dining room chair without using your hands or any other help.



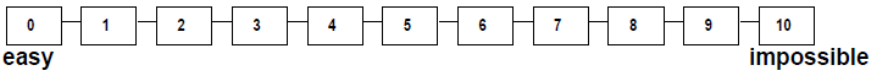
5.5. Getting up off the floor without help from lying on your back.



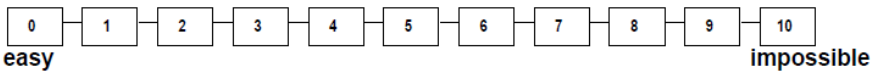
5.6. Standing unsupported for 10 minutes without discomfort.



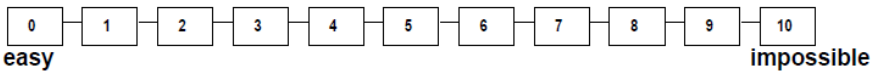
5.7. Climbing 12-15 steps without using a handrail or walking aid. One foot at each step.



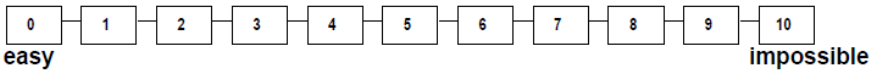
5.8. Looking over your shoulder without turning your body.



5.9. Doing physically demanding activities (e.g. physiotherapy exercises, gardening or sports).



5.10. Doing a full days activities, whether it be at home or at work.



6. ASQol

Please read each statement carefully. We would like you to tick 'yes' if the statement applies to you, and tick 'no' if it does not.

Tick the **one** response that applies best to you **at the moment**.

6.1.	My condition limits the places I can go.	☐ No	☐ Yes
6.2.	I sometimes feel like crying.	☐ No	☐ Yes
6.3.	I have difficulty dressing.	☐ No	☐ Yes
6.4.	I struggle to do jobs around the house.	☐ No	☐ Yes
6.5.	It's impossible to sleep.	☐ No	☐ Yes
6.6.	I am unable to join in activities with my friends / family.	☐ No	☐ Yes
6.7.	I am tired all the time.	☐ No	☐ Yes
6.8.	I have to keep stopping what I am doing to rest.	☐ No	☐ Yes
6.9.	I have unbearable pain.	☐ No	☐ Yes
6.10.	It takes a long time to get going in the morning.	☐ No	☐ Yes
6.11.	I am unable to do jobs around the house.	☐ No	☐ Yes
6.12.	I get tired easily.	☐ No	☐ Yes
6.13.	I often get frustrated.	☐ No	☐ Yes
6.14.	The pain is always there.	☐ No	☐ Yes
6.15.	I feel I miss out on a lot.	☐ No	☐ Yes
6.16.	I find it difficult to wash my hair.	☐ No	☐ Yes
6.17.	My condition gets me down.	☐ No	☐ Yes
6.18.	I worry about letting people down.	☐ No	☐ Yes

NAME:_____ DATE:_____ VISIT #: _ _ SITE #: ___ STUDY # : _____ ★

Questionnaire 1: HEALTH ASSESSMENT QUESTIONNAIRE

INSTRUCTIONS: In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add comments on the back of this page.

Please check (√) the response which best describes your usual abilities **OVER THE PAST WEEK**:

DRESSING AND GROOMING: .....are you able to:	Without **ANY** Difficulty	With **SOME** Difficulty	With **MUCH** Difficulty	**UNABLE** To Do
Dress yourself, including tying shoelaces and doing buttons?				
Shampoo your hair?				
ARISING: .....are you able to:	Without **ANY** Difficulty	With **SOME** Difficulty	With **MUCH** Difficulty	**UNABLE** To Do
Stand up from a straight chair?				
Get in and out of bed?				
EATING: .....are you able to:	Without **ANY** Difficulty	With **SOME** Difficulty	With **MUCH** Difficulty	**UNABLE** To Do
Cut up your meat?				
Lift a full cup or glass to your mouth?				
Open a new carton of milk?				
WALKING: .....are you able to:	Without **ANY** Difficulty	With **SOME** Difficulty	With **MUCH** Difficulty	**UNABLE** To Do
Walk outdoors on fl at ground?				
Climb up five steps?				

Please check (√) any **AIDS** or **DEVICES** that you usually use for any of these activities:			
	Cane		Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)
	Walker		Built up or special utensils
	Crutches		Special or built up chair
	Wheelchair		Other (Specify:_____)
Please check any categories for which you usually need **HELP FROM ANOTHER PERSON**:			
	Dressing and Grooming		Eating
	Arising		Walking

Please check (√) the response which best describes your usual abilities **OVER THE PAST WEEK**:

HYGIENE: ……are you able to:	Without **ANY** Difficulty	With **SOME** Difficulty	With **MUCH** Difficulty	**UNABLE** To Do
Wash and dry your body?				
Take a tub bath?				
Get on and off the toilet?				
REACH: ……are you able to:	Without **ANY** Difficulty	With **SOME** Difficulty	With **MUCH** Difficulty	**UNABLE** To Do
Reach and get down a 5 pound object (such as a bag of sugar) from just above your head?				
Bend down to pick up clothing from the floor?				
GRIP: ……are you able to:	Without **ANY** Difficulty	With **SOME** Difficulty	With **MUCH** Difficulty	**UNABLE** To Do
Open car doors?				
Open jars which have been previously opened?				
Turn faucets on and off?				
ACTIVITIES: ……are you able to:	Without **ANY** Difficulty	With **SOME** Difficulty	With **MUCH** Difficulty	**UNABLE** To Do
Run errands and shop?				
Get in and out of a car?				
Do chores such as vacuuming or yard-work?				

Please check (√) any **AIDS** or **DEVICES** that you usually use for any of these activities:			
	Raised toilet seat		Bathtub bar
	Bathtub seat		Long-handled appliances for reach
	Jar opener (for jars previously opened)		Long-handled appliances in bathroom
	Other (Specify:_____)		
Please check any categories for which you usually need **HELP FROM ANOTHER PERSON**:			
	Hygiene		Gripping and opening things
	Reach		Errands and chores

We are also interested in learning whether or not you are affected by pain because of your illness. How much **pain** have you had because of your illness **IN THE PAST WEEK**:

PLACE A MARK ON THE LINE TO INDICATE THE **SEVERITY OF THE PAIN**

0 ——————————————————————— **100**

NO PAIN (0) SEVERE PAIN (100)

Please check (√) the response which best describes your usual abilities **OVER THE PAST WEEK**:

ACTIVITIES: ……are you able to:	Without **ANY** Difficulty	With **SOME** Difficulty	With **MUCH** Difficulty	**UNABLE** To Do
Carry heavy packages such as grocery bags?				
Sit for long periods of time, such as at work?				
Work at a flat topped table or desk?				
DRIVING A CAR (Check here_____if you **DO NOT** drive): ……are you able to:	Without **ANY** Difficulty	With **SOME** Difficulty	With **MUCH** Difficulty	**UNABLE** To Do
Look in the rear view mirror?				
Turn your head to drive in reverse?				

How much **stiffness** have you had because of your illness **IN THE PAST WEEK**:

PLACE A MARK ON THE LINE TO INDICATE THE **SEVERITY OF THE STIFFNESS**

0 ——————————————————————— **100**

NO STIFFNESS (0) **SEVERE STIFFNESS (100)**

Spinal mobility measures

	Right	Left	Mean/total	BASMI points
Tragus to wall				
Lumbar side flexion				
Modified Schober test				
Cervical rotation				
Intermalleolar distance				
	Total BASMI points (out of 50)			
	BASMI score (total points ÷ 5)			
Chest expansion				

Calculating the BASMI

The result of each assessment is assigned a score according to the table below. Adding up all the scores will provide a total out of 50. This is divided by 5 to give the BASMI score. **The higher (nearer 10) the BASMI score the more severe the patient's limitation of movement due to axial SpA.**

BASMI score calculation table

Points	TTW*	Lateral lumbar flexion*	Modified Schober*	Cervical rotation†	IMD*
0	≤10	≥20	≤7.0	≥85	≥120
1	10-12.9	18-20	6.4-7.0	76.6-85	110-119.9
2	13-15.9	15.9-17.9	5.7-6.3	68.1-76.5	100-109.9
3	16-18.9	13.8-15.8	5.0-5.6	59.6-68	90-99.9
4	19-21.9	11.7-13.7	4.3-4.9	51.1-59.5	80-89.9
5	22-24.9	9.6-11.6	3.6-4.2	42.6-51	70-79.9
6	25-27.9	7.5-9.5	2.9-3.5	34.1-42.5	60-69.9
7	28-30.9	5.4-7.4	2.2-2.8	25.6-34	50-59.9
8	31-33.9	3.3-5.3	1.5-2.1	17.1-25.5	40-49.9
9	34-36.9	1.2-3.2	0.8-1.4	8.6-17	30-39.9
10	≥37	≤1.2	≥0.7	≤8.5	≤30

* Measurement in cm; † measurement in degrees IMD, Intermalleolar distance; TTW, tragus to wall.

Appendix E Patient information leaflets and consent forms

E1 Patient information leaflet – Studies 2-4

E2 Patient consent form – Studies 2-4

E3 Consent to contact form – Studies 2-4

E4 Patient information leaflet – Study 1

Patient Information Leaflet

Title of Research Study:
Osteoporosis in Axial Spondyloarthropathy: epidemiology, measurement techniques, risk factors and biomarkers.

Introduction
Axial spondyloarthropathy (axSpA) is a type of arthritis mainly affecting the spine. Osteoporosis is a disease which makes the bones more fragile and prone to fracture. It occurs at an earlier age in patients with axSpA, but it can be difficult to diagnose. The main aim of the study is to look at ways to diagnose osteoporosis accurately in patients with axSpA. This will give us valuable information to better understand how to detect this disease at an earlier stage.

Why have I been chosen?

1. You have a diagnosis of axial spondyloarthropathy. (This is a chronic form of arthritis that mainly affects the spine)
2. You are a patient of St James's Hospital or Tallaght Hospital
3. You are aged 18 or over

What is the procedure?
As part of this study, you will be asked to attend St James's Hospital:

1. To have a dual x-ray absorptiometry (DEXA) scan to look for osteoporosis. The DXA machine sends a thin invisible beam of low-dose x-rays through the bones. For the examination, you will be lying on a table. The test takes between 10 and 30 minutes.
2. To have an ultrasound examination of the heel to look for osteoporosis, which takes less than 5 minutes.
3. To give a once off blood sample for routine bloods and bone turnover markers.
4. To undergo a routine physical examination and assessment of disease activity (questionnaire and measurements, as performed at each clinic visit).
5. To have updated x-rays of your spine.

All of these procedures are part of your routine care. The bloods and assessment of disease activity will be done in the one visit. Your medical chart will also be looked at to gather details of your medical background by the principal investigator or a doctor designated by him.

Are there any benefits from my participation?
The study is hoping to identify more accurate ways to detect osteoporosis, which will be of benefit to all patients with axSpA. You will also receive an up-to-date assessment for osteoporosis.

Are there any risks involved in participating?

DEXA scans are part of the standard care for axSpA patients. It involves radiation and for this study, the amount of radiation exposure is very slightly higher than a routine scan. You should not have it done if you are pregnant, breast-feeding or trying to conceive. However, the total amount of radiation is similar to what we experience on a day-to-day basis from the environment and doesn't pose any risk to your health. Taking blood from a vein in your arm is also part of routine clinical care and although you may experience discomfort, pain or bruising, these effects should be minimal. No additional risks to you are foreseen from participating in this study.

Are there any exclusions to being in the study?

Patients who are under the age of 18, have dementia, are pregnant or breast-feeding or trying to conceive are not suitable to take part in this study.

What happens if I do not agree to participate in the study?

If you decide not to participate in this study your treatment will not be affected in any way. You will continue to be seen in the dedicated Rheumatology clinics.

Confidentiality

Your identity will remain confidential. A study number will identify you. Your name will not be published or disclosed to any party other than the Principal Investigator and their staff. Direct access to your records by designated medical staff of St James's Hospital or Tallaght Hospital will be needed to check the information collected for the study.

Compensation

Your study doctors are covered by a standard clinical indemnity scheme. If you believe that you have a research related injury it is advised that you should discuss this with your study doctor. Nothing in this document restricts or curtails your rights.

Voluntary Participation:

You have volunteered to participate in this study. You may quit at any time. If you decide not to participate, or if you quit, you will not be penalised and will not give up any benefits which you had before entering the study.

Stopping the study

You understand that your doctor may stop your participation in the study at any time without your consent.

Cost and renumeration

Your participation in this study will not cost you any additional money. You will not receive any payment for participation in this study or for any results derived from the study.

Who is organising and funding this research?

The overall study is organised by Dr. Barry O'Shea, Consultant Rheumatologist, St James's Hospital. Dr Gillian Fitzgerald, co-investigator, has been awarded a scholarship from Abbvie Pharmaceuticals to undertake this research. The research is otherwise not being funded.

Permission

Tallaght Hospital/St James's Hospital Joint Research Ethics Committee have reviewed and approved this study.

Further information

You can get more information or answers to your questions about the study, your participation in the study, and your rights, by contacting:

Principal Investigator:
Dr. Barry O Shea, Consultant Rheumatologist, St James's Hospital Telephone: 087 9405269

Co-investigator:
Dr Gillian Fitzgerald, Rheumatology Specialist Registrar, St James's Hospital Telephone: 087 9405269
E-mail: GiFitzgerald@stjames.ie

CONSENT FORM

Title of Research Study:
Osteoporosis in Axial Spondyloarthropathy: epidemiology, measurement techniques, risk factors and biomarkers.

- This study and this consent form have been explained to me.
- My doctor has answered all my questions to my satisfaction.
- I believe I understand what will happen if I agree to be part of this study.
- I have read, or had read to me, this consent form.
- I have had the opportunity to ask questions and all my questions have been answered to my satisfaction.
- I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights.
- I understand that I am free to leave the study at any point without giving a reason and without this affecting my future care.
- I have received a copy of this agreement.

PARTICIPANT'S NAME: _____

PARTICIPANT'S SIGNATURE: _____

Date: _____

Date on which the participant was first furnished with this form: _____

Where the participant is capable of comprehending the nature, significance and scope of the consent required, but is physically unable to sign written consent, signatures of two witnesses present when consent was given by the participant to a registered medical practitioner treating him or her for the illness.

NAME OF FIRST WITNESS: _____SIGNATURE:_____

NAME OF SECOND WITNESS:_____SIGNATURE: _____

Statement of investigator's responsibility: I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Physician's signature: _____

Date: _____

(Keep the original of this form in the participant's medical record, give one copy to the participant, keep one copy in the investigator's records).

CONSENT TO CONTACT FOR RESEARCH PURPOSES

Study: **Osteoporosis in axial spondyloarthropathy: epidemiology, measurement techniques, risk factors and biomarkers.**

Organisations: St James's Hospital and Tallaght Hospital

Investigators:

- Principal Investigator: Dr Barry O' Shea, Consultant Rheumatologist
- Co-investigators: Prof David Kane, Consultant Rheumatologist
  Dr Ronan Mullan, Consultant Rheumatologist
  Dr Gillian Fitzgerald, Rheumatology Specialist Registrar

You are being invited to give consent for Dr. Barry O' Shea, Dr. Gillian Fitzgerald or a qualified member of the study team to contact you at some time in the future to invite you to participate.

Are you willing to learn more about the study? YES NO

If yes, you will be contacted at a later date. Please include your contact information below:

☐ Telephone number: _____

☐ E-mail address (if desired): _____

You authorize your health service provider to disclose your name and phone number to the research team for the purpose of being contacted to learn more about the research study.

Every effort will be made to safeguard your contact information. Although access to this information will be limited, there is a small chance that this information could be inadvertently disclosed or inappropriately accessed.

You have been made aware of the reasons why the contact information is needed and the risks and benefits of consenting or refusing to consent. This consent is effective immediately. However, your consent to be contacted can be revoked by you at any time.

Patient's Signature: _____

Date: _____

Clinician's Name: _____

Version 2 (updated Aug 2017)

Print Ist page on hospital headed paper

PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE:
Ankylosing Spondylitis Registry of Ireland (ASRI)

NAME OF PRINCIPAL INVESTIGATOR:

You are invited to participate in a research study. Thank you for taking time to read this.
It is important that you read and understand the following information concerning the study before you consent to participate. You should be satisfied that all your questions concerning this study are answered and that you understand your rights as a study patient

WHAT IS THE PURPOSE OF THIS STUDY?

The main aim of the study is to establish an all Ireland registry of patients with Ankylosing Spondylitis (AS). This will include adult patients who have been diagnosed with AS and have been reviewed in a hospital setting within the past 3 years.
This database of patients will facilitate clinical and research studies to allow us to better understand the disease and measure its impact on those who suffer from this disease.

WHY HAVE I BEEN CHOSEN?

You have been chosen because you have a diagnosis of Ankylosing Spondylitis (AS). (This is a chronic form of arthritis that mainly affects the spine)

WHAT WILL HAPPEN IF I VOLUNTEER?

You are asked to carefully read this information leaflet and consent form. The doctor will ask you if you understand all aspects of the study and what is involved for you.

Your participation is entirely voluntary. If you initially decide to take part you can subsequently change your mind without difficulty. This will not affect your future treatment

Put Version and date in here ie Version 1 dated 1/11/2013
Page 1 of

in any way .If you agree to participate, you will be asked to sign the attached consent form, ~~You~~ will have a routine physical examination.
You will be asked to give a once off blood sample of approximately (1 tablespoon) of blood for genetic studies.
You will be asked to complete some questionnaires to assess your pain level, your disease activity and your physical function.
Results of the study will not be available to individual participants.

ARE THERE ANY BENEFITS FROM MY PARTICIPATION?
There is no direct benefit to you in participating in this ~~study~~ but the knowledge gained from this study may be of help to other patients in the future.

ARE THERE ANY RISKS INVOLVED IN PARTICIPATING?
There will be no risks other than those associated with taking blood from a vein in your arm, which you would be having as part of your standard care. These are discomfort, pain or bruising. No additional risks to you are foreseen from participating in this study.

WHAT HAPPENS IF I DO NOT AGREE TO PARTICIPATE?
If you decide not to participate in this study your treatment will not be affected in any way. You will continue to be seen in the dedicated Rheumatology clinics.

CONFIDENTIALITY
Your identity will remain confidential. A study number will identify you. Your name will not be published or disclosed to any party other than the Co-Principal Investigators and their staff.
It is a requirement that your involvement in this study is noted in your medical records. Direct access to your records by medical staff of **HOSPITAL NAME** will be needed to check the information collected for the study.

By signing this consent form you authorise access to this confidential information by the medical staff of **Hospital** for the purpose of this study.

The confidentiality of your medical records will be maintained to the extent permitted by the applicable laws. If results of the study are published your identity will remain confidential.

You have the right of access to and the right to correction of your medical records upon written request to one of the Investigators at **address here**

Put Version and date in here ie Version 1 dated 1/11/2013
Page 1 of

COMPENSATION

Your study doctors are covered by a standard clinical indemnity scheme. If you believe that you have a research related injury it is advised that you should discuss this with your study doctor.

COSTS AND REIMBURSEMENT

Your participation in this study will not cost you any additional money. You will not receive any payment for participation in this study or for any results derived from the study.

WHO IS ORGANISING AND FUNDING THIS RESEARCH?

The overall study is organised by Dr. Barry O'Shea, Consultant Rheumatologist, St James's Hospital, there is a nominal fee paid to each Investigator participating to cover administration costs. The overall project is being funded by a grant from Abbott Pharmaceuticals and Pfizer Pharmaceuticals.

IS THIS STUDY SAFE AND BENEFICIAL?

NAME OF ETHICS GROUP, Ethics and Medical Research Committee have reviewed and approved this study.

FUTURE STUDIES

I give permission for my sample and information collected about me to be stored for possible future research related to this study (including DNA studies) without my further consent being required and subject to approval by a Research Ethics Committee.

Or

I give permission for my samples and information collected about me to be stored for possible future research related to this study (including DNA studies) but only if my consent is obtained at the time for this future research and the research is approved by a Research Ethics Committee

Delete as appropriate

HAS THIS STUDY BEEN REVIEWED BY AN ETHICS COMMITTEE?

The St. Vincent's Healthcare Group, Ethics and Medical Research Committee have reviewed and approved this study.

CONTACT DETAILS or further information or in the event of any adverse event, please contact the number below from 0900-1700 (Monday-Friday) and ask to

speak contact name and details

Put Version and date in here ie Version 1 dated 1/11/2013
Page 1 of

The Participant must complete this form himself/herself.

PLEASE INITIAL YOUR RESPONSE IN THE APPROPRIATE BOX

- I have read and understood the attached Participant Information Leaflet YES ☐ NO ☐

- I have had the opportunity to ask questions and discuss the study and I understand that I may ask further questions at any time. YES ☐ NO ☐

- I understand that my study doctor will endeavour to answer any questions I may have during the study, however if my data has been anonymised it may not always be possible for them to do so YES ☐ NO ☐

- I have received satisfactory answers to all my questions YES ☐ NO ☐

- I have received enough information about this study and the informed consent procedure YES ☐ NO ☐

- I understand that I will not benefit financially if this study leads to the development of a new treatment or medical test YES ☐ NO ☐

- I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care YES ☐ NO ☐

- I agree that the samples I have given and the Information gathered about me can be anonymised and stored for use in future projects relating to Ankylosing Spondylitis **without** further consent being required and subject to the research being approved by a Research Ethics Committee.

YES ☐ NO ☐

Put Version and date in here ie Version 1 dated 1/11/2013
Page 1 of

- I agree to take part in the study YES ☐ NO ☐

Participant's Signature: _____ Date: _____

Participant's Name in print: _____

Investigator's Signature: _____ Date: _____

Put Version and date in here ie Version 1 dated 1/11/2013
Page 1 of

Appendix F Search strategy – Study 5

Interventions (both pharmacological and non-pharmacological) for managing bone health in axial spondyloarthropathy/ankylosing spondylitis

EMBASE

1. 'spondylitis'/de OR 'ankylosing spondylitis'/exp OR 'spondylarthritis'/exp OR 'psoriatic arthritis'/exp
2. ((Ankylo*) NEAR/5 (spondyl* OR spondil* OR spine OR spinal)):ti,ab
3. (Bechterew* OR Bekhterev* OR Marie-Struempell OR spondylarthritis OR spondylarthrosis):ti,ab
4. (axial NEAR/2 spondyloarthropath*):ti,ab
5. #1 OR #2 OR #3 OR #4
6. 'bone strength'/exp OR 'bone mass'/exp OR 'bone density'/exp
7. (Bone* NEAR/3 (health* OR strength OR strong OR improve* OR mass OR densit*)):ti,ab
8. #6 OR #7
9. #5 AND #8

Medline (OVID)

1. exp Spondylitis/
2. ((Ankylo*) adj5 (spondyl* OR spondil* OR spine OR spinal)).ti,ab.
3. (Bechterew* OR Bekhterev* OR Marie-Struempell OR spondylarthritis OR spondylarthrosis).ti,ab.
4. (axial adj2 spondyloarthropath*).ti,ab.
5. or/1-4
6. Bone Density/
7. (Bone* adj3 (health* OR strength OR strong OR improve* OR mass OR densit*)).ti,ab.
8. or/6-7
9. and/5,8

CINAHL

1. (MH "Spondylarthritis+") OR (MH "Spondylosis+")
2. TI ((Ankylo*) N5 (spondyl* OR spondil* OR spine OR spinal)) OR AB ((Ankylo*) N5 (spondyl* OR spondil* OR spine OR spinal))
3. TI (Bechterew* OR Bekhterev* OR Marie-Struempell OR spondylarthritis OR spondylarthrosis) OR AB (Bechterew* OR Bekhterev* OR Marie-Struempell OR spondylarthritis OR spondylarthrosis)
4. TI (axial N2 spondyloarthropath*) OR AB (axial N2 spondyloarthropath*)
5. S1 OR S2 OR S3 OR S4
6. (MH "Bone Density")

7. TI (Bone* N3 (health* OR strength OR strong OR improve* OR mass OR densit*)) OR AB (Bone* N3 (health* OR strength OR strong OR improve* OR mass OR densit*))
8. S6 OR S7
9. S5 AND S8

Cochrane Library (CENTRAL)

1. [mh “Spondylitis”]
2. ((Ankylo*) NEAR/5 (spondyl* OR spondil* OR spine OR spinal)):ti,ab,kw
3. (Bechterew* OR Bekhterev* OR “Marie-Struempell” OR spondylarthritis OR spondylarthrosis):ti,ab,kw
4. (axial NEAR/2 spondyloarthropath*):ti,ab,kw
5. #1 OR #2 OR #3 OR #4
6. [mh “Bone Density”]
7. (Bone* NEAR/3 (health* OR strength OR strong OR improve* OR mass OR densit*)):ti,ab,kw
8. #6 OR #7
9. #5 AND #8

Web of Science

TS=((((Ankylo*) NEAR/5 (spondyl* OR spondil* OR spine OR spinal)) OR (Bechterew* OR Bekhterev* OR Marie-Struempell OR spondylarthritis OR spondylarthrosis) OR (axial NEAR/2 spondyloarthropath*)) AND (Bone* NEAR/3 (health* OR strength OR strong OR improve* OR mass OR densit*)))