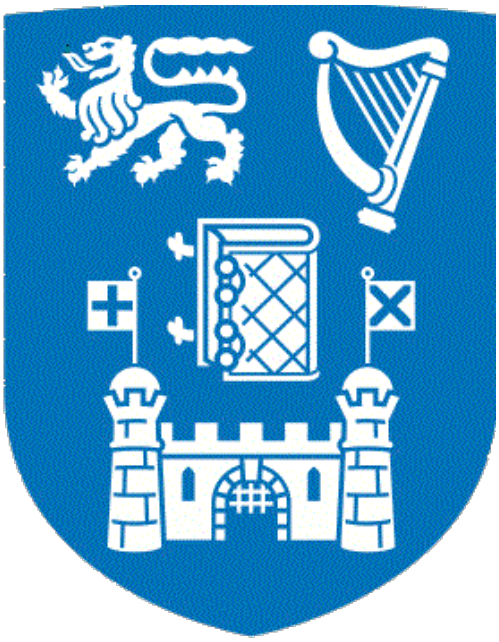
Characteristics and Outcomes of Older Adults Following Distal Forearm Fracture



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Máire Rafferty

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Abstract

Introduction

Osteoporosis and fragility fractures pose a serious public health challenge in our ageing society. Systems are being developed in Ireland and internationally to provide, coordinated and comprehensive assessments and multidisciplinary, evidence-based interventions in patients presenting with fragility fractures. An evidence gap exists regarding both patient outcomes and their predictors following these fractures. Distal forearm fracture (DFF) includes fracture of the distal radius and/or ulna and is one of the most common fragility fracture sites. Vertebral fractures also comprise a large proportion of fragility fractures. Understanding the characteristics of these patients can help in planning and developing appropriate systems of care. Exploring factors that affect patient outcomes will enhance the current evidence base and may help in the development of more targeted pathways to improve clinical outcomes.

Aims

(a) To examine in detail the characteristics of patients with distal forearm fracture who attended the Bone Health Unit at St James's Hospital.

(b) To examine in detail the characteristics of patients with (1) vertebral fracture(s) and (2) both vertebral and distal forearm fracture(s) attending the above unit.

(c) To prospectively investigate the characteristics of patients following a low trauma distal forearm fracture presenting to St James's Hospital.

(d) To assess outcomes (clinical and other) in the above prospective cohort and study the factors related to these outcomes.

Methods

This thesis included three interlinked studies. Study one (discussed in chapter 2) was a cross-sectional study of patient characteristics with a history of distal forearm fracture (DFF) on their first presentation to the bone health clinic. Study two (discussed in chapter 3) was also cross-sectional and looked at patients with a history of vertebral fracture (VF) on their first presentation to the same clinic. Data was collated regarding demographics, medical history, biophysical measures and bone health assessments (DXA, QUS heel, bone turnover markers- BTM) and relationships were explored. Similarities and differences between those with DFF and VF or both fractures were examined.

Study three (discussed in chapters 4, 5 and 6) is a prospective cohort study of all patients presenting to St James's Hospital, Dublin with DFF between January and October 2018 and assessed participants soon after their fracture and again at six and twelve months. The first visit included a 90 minute in person assessment of falls and bone health, as well as recording of medical history, Charlson Comorbidity Index (CCI), dietary calcium intake, and assessment of Mini Mental State Examination (MMSE), frailty and biophysical measures (weight, height, timed up and go (TUG), grip strength, lying and standing blood pressure, DXA, QUS heel, bone turnover markers (BTM's) and other blood tests). Patient reported outcomes measures (PROMS) were assessed using standardized measures including the Patient Rated Wrist Evaluation (PRWE), Disability of the Arm, Shoulder and Hand (DASH) and the Short Form 12 (SF12) at all three visits. Other outcomes were recorded including time not working or driving, falls and fracture, need for initial or future hospital admission, medication adherence and changes in other factors related to bone health (exercise, dietary calcium, vitamin D and BTMs). Non-attendance and death were also recorded.

Results

In the first two studies, we identified a total of 1724 patients with DFF and 1779 with VF, of whom 426 had both fractures. Most patients were female and this was more likely in those with DFF versus VF (86.3% vs 73.1% P=0.000). Those with DFF vs VF were younger (66.3 vs 71.5 years, P=0.000) and had a lower rate of polypharmacy (33.5% vs 47.8%, P=0.000). Prevalence of densitometric osteoporosis varied and was 56.4% with DFF only, 57.2% VF only and 62.6% with both fractures. Only 10% with a single fracture had normal BMD and only 5% with both fractures. Patients with lower BMD were more likely be older, female and have lower BMI. We also noted that 48.3% of DFF patients with a normal DXA had an QUS calculated T score below -1.0. More than half of the patients with both fractures were not taking anti-osteoporosis medication highlighting a significant 'treatment gap'.

In the prospective cohort study, there were 133 patients, and data were available for 87% (n=116) at one year follow up. At baseline, 93.2% were female and mean age was 69.3 years. Almost one in five had a CCI > 4 and 25% were frail. Over a third had polypharmacy and 40% had densitometric osteoporosis with only 10% having normal BMD. DXA forearm identified a further 15% (74/132) with BMD in the osteoporotic range. Factors associated with a diagnosis of osteoporosis included frailty, low BMI, low dietary calcium intake and reduced grip strength. Almost half (45.9%) had a history of previous fracture and 39.8% reported early menopause (< 45 years). About one quarter reported $\geq$ 2 falls in the previous year and the same proportion had orthostatic

hypotension. Two thirds (67.7%) of patients were started on a new antiresorptive medication while 9% continued their current osteoporosis therapy. There were significant improvements at year in exercise levels (21.1% reported doing more), dietary calcium intake (increased by 14.2%) and bone turnover markers (reduction of CTX by 54.2%).

Two patients were in hospital at the time of their DFF, though a further 33 (24.8%) were admitted for surgery for their fracture. Excluding these patients, an additional 18 required admission for $>$ 2 days and their median length of stay was 48 days. These patients were older, had higher rates of polypharmacy, multimorbidity, frailty, cognitive impairment and functional dependence. They were also more likely to have sustained another injury at presentation, and have a history of vertebral fracture(s) and lower BMD. Despite this, only four of these patients were discharged to long-term care and a further seven required significant home supports. There were four incident fractures and four deaths in the year after DFF. However, 26 (19.5%) required subsequent hospitalisation and these patients were more likely to be frail, anaemic and have multimorbidity

I identified a significant improvement in PROMs in the first year following DFF, especially in the first six months. Half of the participants (56 /111) were pain free at 12 months as reported on PRWE. However, only 5 (5.4%) had no disability at one year (as reported on DASH). Factors associated with poorer outcomes included dominant hand fracture, older age, female sex, frailty, polypharmacy, lower BMD, previous fracture, and hospital admission at the time of the fracture.

Discussion

This is the largest study in Ireland to characterize patients with DFF and the only one to prospectively follow up and assess outcomes over a one-year period post fracture. Results highlight the high prevalence of low bone mass and osteoporosis in patients with fragility fractures of the wrist and spine. Between 12.8-24.0% of patients with DFF had a history of vertebral fracture. The role of DXA with vertebral fracture assessment (VFA) to appropriately evaluate these patients as well as the need for specialist services and anabolic therapy needs to be considered. An important finding were the low rates of prior and current treatment with anti-osteoporosis medication (12.8% in study 3, 37.5% in study 1 and 44.4 % in study 2), This highlights a “treatment gap” between those eligible for and actually on treatment, and the need for robust FLS, fracture/falls risk assessment and interventions at or soon after fracture presentation. Indeed, the rate of incident fracture in this study was low at (3%) but this might be in part accounted for by

the high proportion started on anti-osteoporosis medication and good compliance with therapy.

A research gap in older adult trauma is the lack of evidence regarding patient outcomes following fragility fractures. I found significant improvement in patient reported outcomes, especially over the first six months post DFF. Factors associated with poorer outcomes included some that were previously reported, However, I also identified other factors correlated with poorer outcomes that have not been examined before, including frailty and recurrent falls. This study is also one of the largest to explore the association between BMD and DFF outcomes and found a significant positive relationship.

As regards health care usage in patients with DFF, I identified that 18/98 (18.4%) not requiring surgery, were admitted to hospital for more than 2 days, at the time of the fracture presentation. However, half had a inpatient length of stay more than 48 days accounting for a total of 1024 bed days and costing an estimated €899,072. Given that these patient were older, physically frailer and cognitively impaired, there may be a role for early geriatrician led multidisciplinary care to optimise their outcomes and facilitate earlier discharge.

Importantly, resulting from my studies the number of fractures identified by the FLS in St James's Hospital was significantly increased as all DFF were captured from x-ray reports as opposed to only patients admitted and recorded on the Hospital In-Patient Enquiry (HIPE) system. I identified a high rate (34.6%) of cancellation and non-attendance for appointments with patients attending after versus within 12 weeks of fracture being more likely to be frail and functionally dependent. The IOF Best practice frameworks for FLS recommend evaluation within 8 weeks for level 3 performance and 12 weeks for level 2 performance, so this has important implications for service planning. In such patients, consideration should be given for telephone or virtual clinics.

Conclusion

Study findings show there is a high prevalence of densitometric low bone mass/osteoporosis in Irish adults with DFF. Furthermore, a high proportion had a history of other fragility fractures though despite this, there was a significant treatment gap. In fact, up to nearly 80% in my cohort study were deemed to need anti-osteoporosis therapy. This highlights the importance of further expansion of FLS throughout Ireland. As a quarter of patients with DFF had recurrent falls and orthostatic hypotension, it should be incorporated into falls risk assessment. Compliance with osteoporosis therapy for patients with DFF was good, likely reflecting the value of follow up appointments

and patient education. 18.4% of patients with DFF were admitted to hospital despite not needing surgical correction of their fracture contributing to a significant number of bed days. These patients were older and frailer, and these factors were also associated with poorer outcomes at one year. For this reason, they are likely to benefit from orthogeriatric care which should be expanded beyond hip fractures patients. This could positively impact clinical outcomes but also might reduce patient length of stay. The recently initiated FLS audit of several pilot hospital sites in Ireland will be important in establishing deficits in key performance indices with regard to fragility fractures and the need for improvements in care.

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Abbreviations

25(OH)D: Serum 25-hydroxycholecalciferol

AACE: American Association of Clinical Endocrinology

ABQ: Algorithm Based Qualitiatve Method

AFF: Atypical Femoral Fracture

ALP: Alkaline Phosphatase

BMD: Bone Mineral Density

BTM: Bone Turnover Markers

BUA: Broadband Ultrasound Attenuation

CKD-MBD: Chronic Kidney Disease- Metabolic Bone Disease

CT: Computed Tomography

CTX: C-terminal telopeptide of type 1 collagen

DALYs: Disability Adjusted Life Years

DASH: Disability of the Arm Shoulder and Hang

DEQAS: Vitamin D External Quality Assessment Scheme

DFF: Distal Forearm Fracture

DRF: Distal Radius Fracture

DXA: Dual X-ray Absorptiometry

EFSA: European Food Safety Authority

eGFR: Estimated Glomerular Filtration Rate

EMA: European Medicines Agency

EU: European Union

FDA: US Food and Drug Administration

FLS: Fracture Liaision Service

FRAX: Fracture Risk Assessment Tool

FSAI: Food Safety Authority of Ireland

HRT: Hormone Replacement Therapy

IHD: Ischaemic Heart Disease

IOF-ESCEO: International Osteoporosis Foundation - European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis

IOF: International Osteoporosis Foundation

IOM: Institute of Medicine

ISCD: International Society of Clinical Densitometry

LCMS: Liquid chromatography mass spectroscopy

MCS 12: Mental Component Scale 12 (derived from SF 12)

MHQ: Michigan Hand Questionnaire

MMSE: Mini Mental State Examination

MOF: Major Osteoporotic Fracture

MR: Magnetic resonance (imaging techniques)

MRONJ: Medication Related Osteonecrosis of the Jaw

NANS: National Adult Nutrition survey

NBHA: National Bone Health Alliance (USA)

NIST: National institute of Standards and Technology

NOGG: National Osteoporosis Guideline Group (UK)

NTX: N-telopeptide of collagen cross links

ONJ: Osteonecroiss of the Jaw

OR: Odds ratio

PCS 12: Physical Component Scale 12 (derived from SF 12)

PINP: Procollagen type 1 N Propeptide

PRI: Population Reference Intake

PROMs: Patient Reported Outcome Measures

PRWE: Patent-Rated Wrist Evaluation

PTH: Parathyroid Hormone

QALY: Quality Adjusted Life Years

QUS: Quantitative Ultrasound

RANK L: Receptor Activator of Nuclear Factor Kappa B Ligand

RANK: Receptor Activator of Nuclear Factor Kappa B

RCT: Randomised Controlled Trial

SERM: Selective oestrogen receptor modulator

SF12: Short Form 12

SIGN: Scottish Intercollegiate Network

SJH: St James's Hospital

SOS: Speed of Sound

SQ method: Semi Quantitative method

TILDA: The Irish Longitudinal Study of Ageing

TUG: Timed up and Go

UK: United Kingdom

VFA: Vertebral Fracture Assessment

WHO: World Health Organisation

List of presentations/publications arising from this work

Rafferty M, Walsh JB, McCarroll K. Characteristics and outcomes of older adults requiring prolonged admission at the time of low trauma wrist fracture: a prospective cohort study. *European Geriatric Medicine* 11, 1- 309.December 2020.

Rafferty M, Fallon N, Steen G, Maher N, Walsh JB, McCarroll K. Characteristics of patients attending a specialist bone health clinic following vertebral fractures. *European Geriatric Medicine* 11, 1-309.December 2020.

Rafferty M, Walsh JB, McCarroll K. A prospective cohort study of patient characteristics, bone health measures and clinical outcomes following low trauma wrist fracture. *Journal of Bone and Mineral Research* Volume 35 Number S1, November 2020. P 1-337

Rafferty M, Fallon N, Steen G, Maher N, O Carroll C, Walsh JB, McCarroll K. The clinical characteristics of patients with wrist fracture attending a bone health unit in Ireland. *Journal of Bone and Mineral Research* Volume 35 Number S1, November 2020. P 1-337

Rafferty M, Walsh JB, McCarroll. Patient characteristics and outcomes at time of distal forearm fracture: A cross sectional study in an Irish hospital. World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO 2020): Poster Abstracts. *Osteoporosis International* **31** (Suppl 1), 133–621 (2020)

Gannon E, **Rafferty M**, Fallon N, O Connell C, Hendy E, Lannon R, McCarroll K. Utility of forearm DXA in the evaluation and management of patients attending a specialist osteoporosis and bone health clinic. World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO 2020): Poster Abstracts. Osteoporos Int. 2020 Dec;31(Suppl 1):133-621.

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Chapter 1: Introduction and literature review

1.1 Introduction

Osteoporosis and fragility fractures are common and have a significant impact on the lives of patients. The number of Disability Associated Life Years (DALYs) associated with fragility fracture was compared to 16 other non-communicable diseases in the EU6. It ranked fourth, outranked only by Ischaemic Heart Disease (IHD), dementia, and lung cancer. (1) Hip fracture and its consequences have been the focus of much research. However, distal forearm and vertebral fractures are very common and may represent a sentinel fracture event that increases the risk of incident hip and other fractures. Despite this, there is need for more studies examining factors contributing to poorer outcomes in these patients and these fractures often remain a missed opportunity for intervention.

In this thesis, I investigated patients who had sustained a distal forearm or vertebral fracture attending a specialist Bone Health Clinic in St James's Hospital Dublin. I collated data on patient clinical characteristics, bone health and fracture history and biophysical assessments.

I also investigated a prospective cohort of patients attending the hospital with distal forearm (wrist) fractures. I examined patient characteristics, demographics, risk factors and secondary causes of osteoporosis, measures of bone health and also osteoporosis diagnosis by DXA criteria. In this cohort I also identified bone health treatments, compliance and factors associated with patient outcomes including quality of life measures.

1.2 Osteoporosis

Osteoporosis is a skeletal disorder characterised by reduced bone mineral density, micro-architectural deterioration in bone and increased risk of fragility fracture. There are two main components of bone strength; bone density and bone quality. Areal bone mineral density (BMD), as measured by Dual-energy Xray Absorptiometry (DXA), is expressed in grams of mineral per unit area (g/cm^2). Bone quality is determined by architecture, turnover, damage accumulation (e.g. microfractures) and mineralization (2).

1.2.1 Prevalence

The prevalence of osteoporosis in Ireland is not known though it is estimated to affect about 300,000 people (3). The Irish Longitudinal Study in Ageing (TILDA) used quantitative ultrasound (QUS) of the heel in adults aged 50 or over and suggested that 3% of men and 13% of woman had osteoporosis (4). Due to an ageing population worldwide, the prevalence of osteoporosis is expected to increase (5). In 2019, 25.5 million women and 6.5 million men were estimated to have osteoporosis in the EU plus Switzerland and the UK (EU27+2) and 4.2 million new fragility fractures. The cost of osteoporosis, including pharmacological intervention in the EU, Switzerland and UK was estimated at €57 billion (6).

1.2.2 Diagnosis and evaluation

There are a number of approaches to the diagnosis of osteoporosis. DXA is the most widely validated technique to measure bone mineral content or BMD. As absorption of x-rays is particularly sensitive to calcium content of the tissue. Results are expressed as grams of mineral per cm^2 measured and then compared to reference populations to determine T scores. A T scores is the number of standard deviations a result is from the mean in a group of healthy young women. WHO criteria were proposed in 1994 and revised in 2007. They suggest four diagnostic categories based on DXA results (7):

- Normal. A value for BMD that is higher than 1 SD below the young adult female reference mean (T-score greater than or equal to –1 SD).
- Low bone mass (osteopaenia). A value for BMD more than 1 SD below the young female adult mean, but less than 2.5 SD below this value (T- score less than -1 and greater than -2.5 SD).
- Osteoporosis. A value for BMD that is 2.5 SD or more below the young female adult mean (T-score less than or equal to –2.5 SD).
- Severe osteoporosis (established osteoporosis). A value for BMD that is 2.5 SD or more below the young female adult mean in the presence of one or more fragility fractures.

The recommended reference range is the NHANES III reference database for femoral neck measurements in women aged 20–29 years.

In recent years other groups have commented on the diagnostic criteria for osteoporosis. The National Bone Health Alliance Working Group in the USA published an updated position paper regarding the clinical diagnosis of osteoporosis in 2014. “We propose the continued use of T-scores as one means for diagnosis but recommend that, alternatively, hip fracture; osteopenia-associated vertebral, proximal humerus, pelvis, or some wrist fractures; or FRAX estimated 10 year fracture risk of ≥3 % for hip or 20 % for major osteoporotic fracture could confer a diagnosis of osteoporosis” (8). In clinical practice, osteoporosis treatment is generally considered in these circumstances. The Fracture Risk Assessment Tool or “FRAX” is a free online tool that estimates fracture risk based on known risk factors with or without inputting BMD. Figure 1 below is a screenshot from the website demonstrating the tool (9).

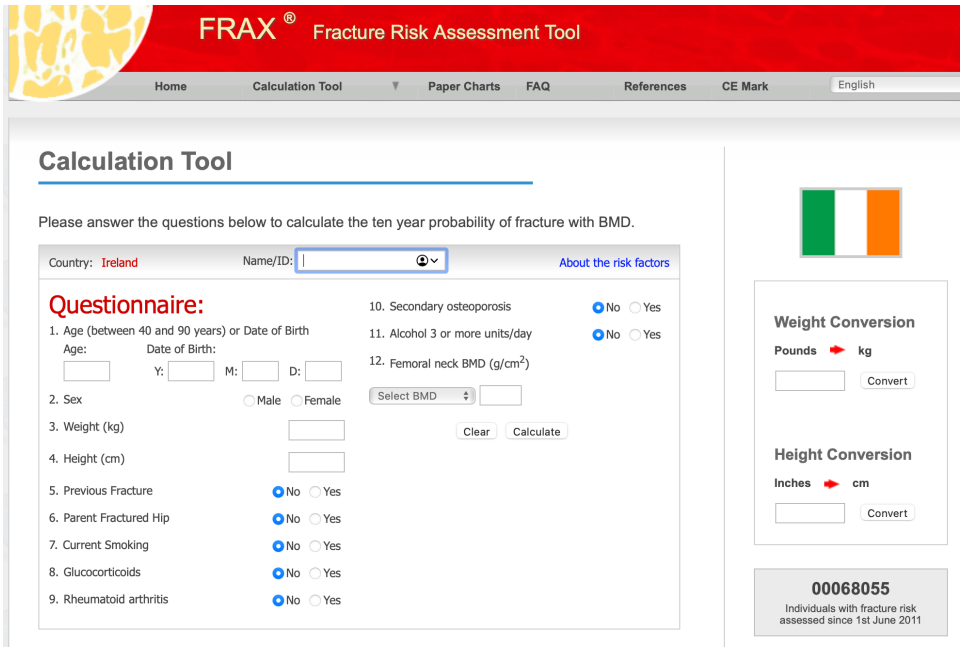


Figure 1: Fracture Risk Assessment Tool data input

DXA

Generally, DXA evaluation of the hip (femoral neck and total hip) and lumbar spine are used and interpreted using WHO T scores definitions (10).There is emerging evidence regarding the role of peripheral DXA including forearm DXA in the evaluation of osteoporosis and fracture risk (11, 12). Commonly reported peripheral DXA forearm sites include the one -third (33%) radius, the ultra-distal (UD) radius and the total radius. At present, the International Society for Clinical Densitometry (ISCD) recommend the use of DXA forearm in specific circumstances such as in patients with primary hyperparathyroidism (where there is cortical bone loss at the forearm) or when there is no other available site for assessment. It is recommended that the report includes acknowledgement of limitations of the test, including a statement that the WHO diagnostic classification cannot be applied to T-scores obtained from pDXA other than one-third (33%) radius measurements (13).

Calcaneal QUS

QUS can also be used as an imaging modality to estimate bone density peripherally (14). Since its introduction as a tool for the evaluation of bone status in 1984, it has become more popular as it is portable, easier to handle than DXA, is lower in cost and is does not emit ionising radiation. The ultrasound is a type of sound wave at high frequency (usually 200kHz – 1.5MHz) produced by piezoelectric probes. The machine usually has two probes and the bone segment to be examined is placed between them. One probe produces and emits the ultrasound waves and the other is a receiver. QUS results are often reported in terms of Speed of Sound (SOS) and Broadband Ultrasound Attenuation (BUA) depending on the axis the ultrasound waves take to travel through the bone. Composite parameters used include Amplitude-Dependent SOS, Stiffness index,

Quantitative Ultrasound index and estimated T score. Many researchers recommend that these measures are more useful. At present the ISCD only recommends calcaneal QUS as a recognised measure of bone status as most studies have looked at measurements at this site. QUS measures reflect information about bone quality (microstructure, anisotropy or elasticity of the mineralised matrix) as well as BMD, however the optimal interpretation of the results has not yet been fully defined. Nonetheless, it is associated with fracture risk and has been shown to be a good predictor of fracture in a number of studies (15). Two large studies, one with 6189 and the other with 14,824 patients showed that QUS at the calcaneus was a good predictor of hip fracture (16, 17). Another study of 2837 women showed a similar association between QUS and central DXA in terms of vertebral fracture risk (18).

Some studies have also looked at how QUS compares with DXA. Two large community based cross-sectional studies found that there was a 40-50% overlap in the number of women in the lowest quartile of both DXA and QUS heel measurements (19) (20). Another showed QUS heel to have a sensitivity of 65-70% for BMD in the lowest quartile (21). In a study looking as osteoporosis according to WHO criteria the sensitivities were higher 69-77% (21). Most recently, a small study looked at sensitivities, predictive values and likelihood ratios of QUS results for DXA diagnosed osteoporosis (22). The authors showed that in 59 patients with low trauma fractures (with a 28% prevalence of osteoporosis by DXA criteria), specificity for predicting BMD defined osteoporosis was high (86%) but sensitivity was low (53%). A QUS result in the osteoporotic range was highly predictive of BMD defined osteoporosis. Positive predictive value was 60% and negative predictive value was 82%.

There is no consensus on what cut-off values to use with QUS to diagnose osteoporosis. The ISCD position paper outlines some of the issues in defining cut-offs in particular due to variations in the device used, differences between manufacturers and in population reference ranges (23). Therefore, currently there is no agreed criteria for diagnosing osteoporosis using QUS though it may be useful as an adjunctive assessment in some patients.

One study has shown that there may be a role for QUS in monitoring treatment response using BUA measurements and Stiffness Index, though this is not recommended and further research is needed (24). Concern also exists regarding the precision of ultrasound measures and the slow rate of change of bone mass at peripheral sites.

Bone turnover markers (BTM)

The use of BTM is expanding in clinical practice. The National Bone Health Alliance (NBHA) in the US, in agreement with International Osteoporosis Foundation (IOF) and International Federation of Clinical Chemistry and Laboratory Medicine IFCC, has endorsed procollagen type 1 N propeptide (PINP), and C-terminal telopeptide of type 1 collagen (CTX), in blood, as reference standard BTMs

(25). They are measured on immunoassay either on an automated platform or by manual assay. CTX is a marker of bone resorption and P1NP of bone formation.

The value of BTM is their association with prediction of bone loss. High bone turnover is associated with more rapid bone loss. High bone turnover is also associated with several types of fracture in both men and women. However, the value of fracture prediction has not been fully established, and BTM are not included in the FRAX algorithm. BTMs can also be used in monitoring of treatment response and providing feedback on adherence and compliance to treatment or suggesting underlying secondary causes (26). IOF have recommended that BTMs within three months of treatment initiation with oral bisphosphonates would help identify poor compliance. BTMs are most commonly used to monitor response to antiresorptive therapies. A decrease from baseline of greater than the 20% for PINP or 30% for CTX confirms response to therapy. An absolute value lower than the median premenopausal value of 35ug/l for PINP and 280ng/l for CTX is also considered a therapeutic target. Monitoring of BTMs during a drug holiday may also be a helpful way of considering when to restart treatment. Use of BTMs in monitoring anabolic therapy usually focuses on PINP as a formation marker. An increase >10ug/l is considered to indicate response though much larger increases are frequently noted (27). More recently, the National Osteoporosis Guideline Group UK (NOGG) have recommended the use of BTMs in decisions regarding transitioning between denosumab and bisphosphonates (28).

Other BTMs are also used clinically and in research. Alkaline phosphatase (both total and bone specific alkaline phosphatase) and Parathyroid Hormone (PTH) are particularly useful in the contest of CKD-MBD and Paget disease. Osteocalcin is another marker of bone formation that is used clinically, often in conjunction with other markers. N-telopeptide of collagen cross links (NTX), derived from serum, plasma or urine samples and Tartrate-resistant acid phosphatase (TRAP 5B) derived from serum or plasma are other markers of resorption.

There can be variance in the measurement of BTMs. A number of factors should be considered to reduce the risk of confounding with BTM samples. These include taking samples in the morning and in a fasted state (25). In particular, the occurrence of a fracture or treatment with glucocorticoids may have a significant impact on BTM measurements. There is a large increase in PINP after a fracture with a mean increase of 55% six weeks after wrist fracture (29), 96% after ankle fracture (30) and 100% 12 weeks after tibial shaft fracture (31). The magnitude of the increase appears to relate to the bone size at the site of fracture and may be greater if the fracture is managed surgically. Glucocorticoid therapy reduces the level of P1NP in a dose dependent manner. Non bone factors can also impact the result e.g. non bone sources of PINP like skin. CTX in particular has kinetic properties that limit its use in CKD (32).

Trabecular Bone Score

Trabecular Bone Score (TBS) was developed as a non-invasive imaging tool to assess skeletal microarchitecture. It is a textural index that evaluates grey level variations in the lumber spine region using DXA images (33). Its clinical uses are being studied in a number of circumstances (34). ISCD published a position paper in 2019 highlighting the role of TBS as an independent predictor of fracture (35). However, it also outlined how TBS is not useful for monitoring the effect of bisphosphonates or denosumab therapy but may have a role in assessing response to anabolic treatments.

Quantitative CT

The role of CT in the evaluation of BMD has grown in recent years. Quantitative CT can be used to assess volumetric as opposed to areal bone mineral density and also provide information on bone microarchitecture (36). ISCD recommends that reports should outline the limitations of the test including a statement that the WHO diagnostic classification cannot be applied to T-scores obtained from QCT (13).

1.2.3 Risk factors for osteoporosis

An estimated 60-80% of the variability in bone mass and osteoporosis risk is explained by heritable factors (37). Genome-wide association studies have identified more than 70 loci associated with adult bone density or fractures (38). Undoubtedly, genetics contribute greatly to the accrual of bone mass, peak bone mass and ultimately the development of osteoporosis (39). Increasing age and female sex are also risk factors for osteoporosis. Almost all studies indicated that increasing age is a strong determinant of BMD and fracture risk independent of BMD (40). Generally, greater age is associated with lower BMD in both sexes and all races. Female gender also is associated strongly with osteoporosis. Oestrogen deficiency is implicated strongly in the disproportionately higher prevalence of osteoporosis in women in particular when there is a short fertile period, surgical menopause or premature menopause (7).

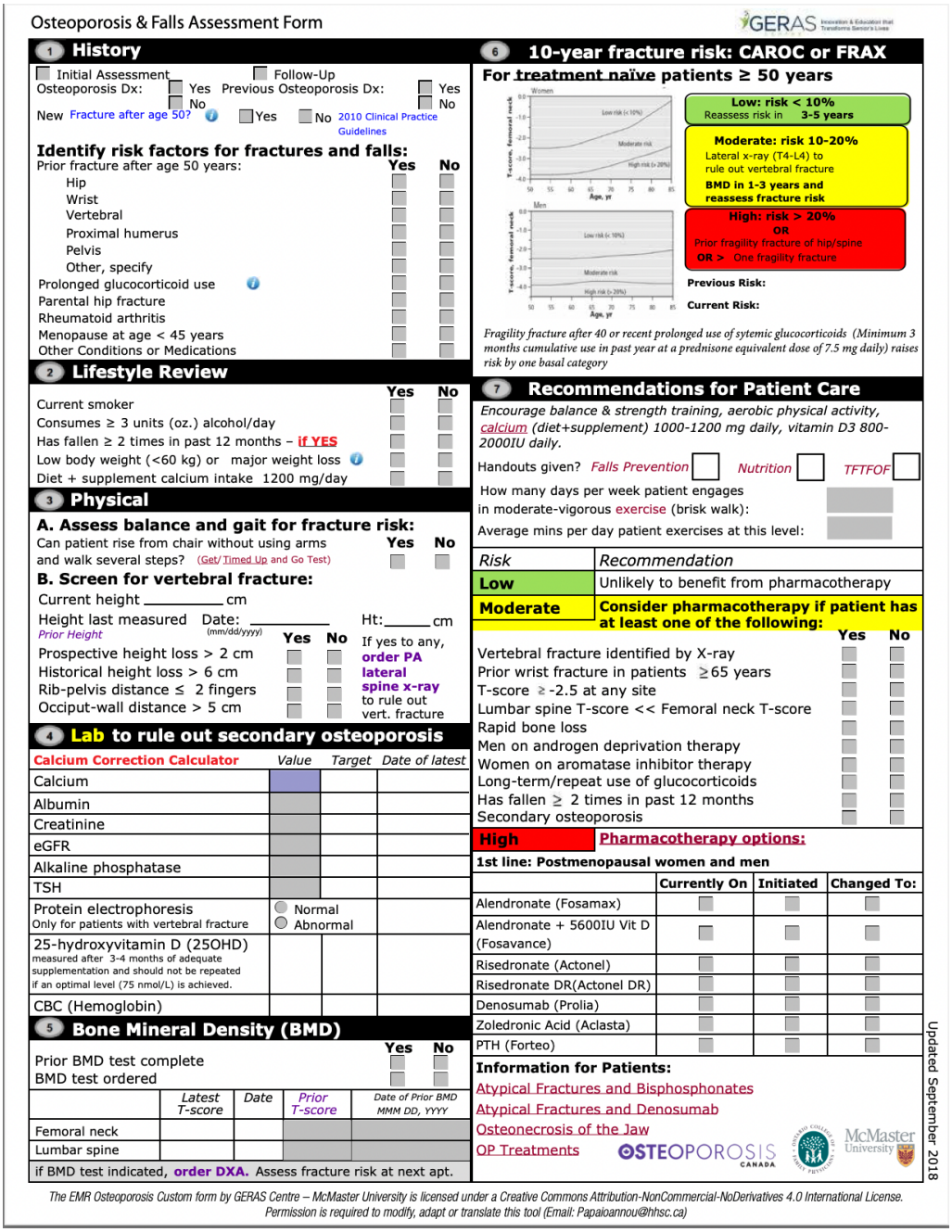
Alcohol intake shows a dose-dependent relationship with fracture risk. When alcohol intake is on average two units or less daily, no increase in risk has been identified. Intakes of 3 or more units daily are associated with a dose-dependent increase in fracture risk (41). In patients with alcohol dependence, fracture risk is reduced following three years of abstinence (42). Smoking has similarly been shown to be associated with reduced BMD and increased fracture risk (43). Risk of hip fracture was reduced in those who had stopped smoking compared to those currently smoking after just five to ten years (44).

Dietary factors and key nutrient deficiencies can be associated with impaired development of optimal peak bone mass. The most important nutrients are calcium, protein, and vitamin D. Low BMI is an important predictor of hip fracture but when adjusted for BMD its value in fracture prediction at other sites is reduced. Even when dietary intake of required nutrients is adequate, absorption can be impaired and contribute to the development of osteoporosis, such as in malabsorptive syndromes, post gastrectomy or with pernicious anaemia. Where exposure to sunlight is limited vitamin D deficiency may be implicated (7).

Other medical conditions can also be risk factors for osteoporosis; endocrinopathies such as hyperparathyroidism, hyperthyroidism, overtreated hypothyroidism, diabetes mellitus, Cushing disease or syndrome, athletic amenorrhoea, anorexia nervosa, Turner and Klinefelter syndromes. Medical conditions associated with oestrogen deficiency and hypogonadism are also implicated including acromegaly, haemochromatosis and chronic liver disease. Other medical conditions associated with osteoporosis include solid organ transplantation and a wide range of gastrointestinal, rheumatological, neurological, haematological (including multiple myeloma) and immunological conditions (45, 46). Inflammatory conditions such as inflammatory bowel and rheumatological diseases are frequent causes of osteoporosis, both due to the conditions themselves and some of the associated treatments.

Medications can also contribute to the development of osteoporosis. Oral glucocorticoid therapy increases fracture risk in a dose-dependent manner. Excess thyroid hormone, aromatase inhibitors for the treatment of breast cancer, androgen deprivation therapy for the treatment of prostate cancer and thiazolidinediones used In the treatment of diabetes have all been shown to increase hip fracture risk (47). Other medications associated with osteoporosis include antidepressants, antiparkinsonian drugs, antipsychotic drugs, anxiolytic drugs, benzodiazepine, proton pump antagonists, H2 receptor antagonists and antiretroviral agents (48). Anticonvulsant medications also appear to hae negative impact on bone density and can interfere with vitamin D metabolism (49).

Many bone health units and fracture liaison services have a standardised approach to screening for the above causes. For example the following form is used in the Canadian FLS (50).



Osteoporosis & Falls Assessment Form

GERAS

1 History

Initial Assessment ☐ Follow-Up

Osteoporosis Dx: ☐ Yes ☐ No

Previous Osteoporosis Dx: ☐ Yes ☐ No

New Fracture after age 50? ☐ Yes ☐ No 2010 Clinical Practice Guidelines

Identify risk factors for fractures and falls:

Prior fracture after age 50 years:	Yes	No
Hip	☐	☐
Wrist	☐	☐
Vertebral	☐	☐
Proximal humerus	☐	☐
Pelvis	☐	☐
Other, specify	☐	☐
Prolonged glucocorticoid use	☐	☐
Parental hip fracture	☐	☐
Rheumatoid arthritis	☐	☐
Menopause at age < 45 years	☐	☐
Other Conditions or Medications	☐	☐

2 Lifestyle Review

	Yes	No
Current smoker	☐	☐
Consumes ≥ 3 units (oz.) alcohol/day	☐	☐
Has fallen ≥ 2 times in past 12 months – if YES	☐	☐
Low body weight (<60 kg) or major weight loss	☐	☐
Diet + supplement calcium intake 1200 mg/day	☐	☐

3 Physical

A. Assess balance and gait for fracture risk:

Can patient rise from chair without using arms and walk several steps? (Get/Timed Up and Go Test) Yes ☐ No ☐

B. Screen for vertebral fracture:

Current height _____ cm

Height last measured Prior Height Date: _____ (mm/dd/yyyy) Ht: _____ cm

	Yes	No
Prospective height loss > 2 cm	☐	☐
Historical height loss > 6 cm	☐	☐
Rib-pelvis distance ≤ 2 fingers	☐	☐
Occiput-wall distance > 5 cm	☐	☐

If yes to any, **order PA lateral spine x-ray** to rule out vert. fracture

4 Lab to rule out secondary osteoporosis

Calcium Correction Calculator	Value	Target	Date of latest
Calcium			
Albumin			
Creatinine			
eGFR			
Alkaline phosphatase			
TSH			
Protein electrophoresis Only for patients with vertebral fracture	○ Normal ○ Abnormal		
25-hydroxyvitamin D (25OHD) measured after 3-4 months of adequate supplementation and should not be repeated if an optimal level (75 nmol/L) is achieved.			
CBC (Hemoglobin)			

5 Bone Mineral Density (BMD)

	Yes	No
Prior BMD test complete	☐	☐
BMD test ordered	☐	☐

	Latest T-score	Date	Prior T-score	Date of Prior BMD MMM DD, YYYY
Femoral neck				
Lumbar spine				

if BMD test indicated, **order DXA.** Assess fracture risk at next apt.

6 10-year fracture risk: CAROC or FRAX

For treatment naïve patients ≥ 50 years

Low: risk < 10%
Reassess risk in **3-5 years**

Moderate: risk 10-20%
Lateral x-ray (T4-L4) to rule out vertebral fracture
BMD in 1-3 years and reassess fracture risk

High: risk > 20%
OR
Prior fragility fracture of hip/spine
OR > One fragility fracture

Previous Risk:

Current Risk:

Fragility fracture after 40 or recent prolonged use of sytemic glucocorticoids (Minimum 3 months cumulative use in past year at a prednisone equivalent dose of 7.5 mg daily) raises risk by one basal category

7 Recommendations for Patient Care

Encourage balance & strength training, aerobic physical activity, calcium (diet+supplement) 1000-1200 mg daily, vitamin D3 800-2000IU daily.

Handouts given? *Falls Prevention* ☐ *Nutrition* ☐ *TFTFOF* ☐

How many days per week patient engages in moderate-vigorous exercise (brisk walk):

Average mins per day patient exercises at this level:

Risk	*Recommendation*
Low	Unlikely to benefit from pharmacotherapy
Moderate	**Consider pharmacotherapy if patient has at least one of the following:**

	Yes	No
Vertebral fracture identified by X-ray	☐	☐
Prior wrist fracture in patients ≥65 years	☐	☐
T-score ≥ -2.5 at any site	☐	☐
Lumbar spine T-score << Femoral neck T-score	☐	☐
Rapid bone loss	☐	☐
Men on androgen deprivation therapy	☐	☐
Women on aromatase inhibitor therapy	☐	☐
Long-term/repeat use of glucocorticoids	☐	☐
Has fallen ≥ 2 times in past 12 months	☐	☐
Secondary osteoporosis	☐	☐

High **Pharmacotherapy options:**

1st line: Postmenopausal women and men

	Currently On	Initiated	Changed To:
Alendronate (Fosamax)	☐	☐	☐
Alendronate + 5600IU Vit D (Fosavance)	☐	☐	☐
Risedronate (Actonel)	☐	☐	☐
Risedronate DR(Actonel DR)	☐	☐	☐
Denosumab (Prolia)	☐	☐	☐
Zoledronic Acid (Aclasta)	☐	☐	☐
PTH (Forteo)	☐	☐	☐

Information for Patients:

Atypical Fractures and Bisphosphonates
Atypical Fractures and Denosumab
Osteonecrosis of the Jaw
OP Treatments

OSTEOPOROSIS CANADA

McMaster University

Updated September 2018

Figure 2 Esample of Osteoporosis and Falls Assessment Form

1.2.4 Management & Treatment of osteoporosis

The goals of treatment are to improve bone mineral density, restore bone microarchitecture, and reduce fracture risk. The evaluation of osteoporosis includes the assessment and treatment of underlying causes as discussed above. In addition, there are specific pharmacological and non-pharmacological treatments.

Non Pharmacological treatments

Non pharmacological approaches in the treatment of osteoporosis includes dietary and lifestyle optimisation. Dietary advice includes optimisation of BMI if under or over weight and maintenance or a healthy balanced diet with adequate calcium and protein intake

Exercise is recommended in the treatment of osteoporosis. In particular, weight bearing exercise and muscle strengthening tailored to the patients' needs and ability. In addition, all patients with osteoporosis should be advised regarding smoking cessation and alcohol consumption. Recent NOGG guidance recommends moderation of alcohol consumption to less than two units a day and smoking cessation (28).

Recent FSAI guidelines were published which recommend a food based dietary guideline for calcium. Daily consumption of three portions of calcium rich foods (such as milk, yogurt and cheese) is recommended in order to meet the requirement in older adults (51). In older adults who consume less than one portion of dairy products daily, a 500mg calcium supplement is recommended. There is some disagreement about the recommended level of calcium intake in older adults. Population reference intake (PRI) for older adults varies from 950mg (EFSA recommendation 2016) (52) to 1200mg (IOM recommendation 2011) (53). NOGG guidance recommends minimum 700mg of calcium a day, preferably achieved through dietary calcium intake (28). In NANS (n=226) average intake for women was 985mg and men 908mg (54). However, a number of cohort studies have shown considerably lower self-reported calcium intake in older adults. In the TUDA cohort study, it was reported that overall, only 3.5% of patients were meeting their daily requirement (55). In TILDA, a nationally representative cohort study, 70% of older adults did not consume the recommended three portions of calcium rich foods (56).

The FSAI report recommended 15-20ug of vitamin D daily. This is difficult to achieve through dietary sources alone. In Ireland, patients are unlikely to meet their daily vitamin D requirement through dietary intake. The prevalence of vitamin D deficiency has been examined in a number of Irish studies. The prevalence of vitamin D deficiency (25(OH)D <30nmol/L) in older Irish adults in The Irish Longitudinal Study of Aging (TILDA) was shown to be 13.1% overall. Vitamin D deficiency was shown to be of particular concern in non-supplement users, in the winter, in smokers, obese adults and the physically inactive, as well as those living alone and those over eighty years of age (57). For

this reason, vitamin D supplementation is recommended for most older adults and for patients with osteoporosis. NOGG recommends that 800 units of vitamin D is prescribed if patients are at risk of insufficiency or have insufficiency identified on assessment (28).

Falls also increase the risk of fracture. Recurrent falls (two or more in the last year) have been shown to increase the probability of fracture by 30% (58). Factors that increase the risk of falling include environmental factors (e.g. uneven surfaces, trip hazards), alterations of gait and balance, conditions associated with transient loss of consciousness, orthostatic hypotension and polypharmacy. A personalised multimodal falls intervention plan should be developed by the multidisciplinary team to reduce the frequency of future falls. Exercise is often recommended to reduce further falls by maintaining or restoring muscle strength, balance and posture, improving confidence and reaction times. However, two RCTs have not demonstrated an effect of multidisciplinary intervention targeted at falls on fracture reduction (59, 60). A Cochrane review of falls prevention exercise programmes, albeit with low certainty, showed evidence of a reduction in fall-related fractures in community dwelling older adults (61). Programmes with combined exercise protocols and for three hours or more a week are more effective. Home safety interventions have also been shown to reduce the risk of falls. The Royal Osteoporosis Society "Strong, Steady, Straight" programme provides evidence-based instruction for patients that can be easily used in a clinical setting (62).

Pharmacological therapy

There are two main modes of action of medications used in the treatment of osteoporosis: drugs that inhibit bone loss (anti-resorptives) or those that simulate new bone formation (anabolic agents).

Antiresorptive therapy

Bisphosphonates

Bisphosphonates are the mainstay of treatment for patients with osteoporosis and are commonly a first line agent. This class of drug inhibits bone resorption by selectively targeting osteoclasts (63).They can be taken orally (alendronate, ibandronate and risedronate) or intravenously (zoledronic acid or ibandronic acid). There is a now a very large evidence base supporting the use of bisphosphonates. Zoledronate is associated with a 70-78% reduction in vertebral fracture risk at 36 months (64). Oral bisphosphonates, in recent meta-analyses, have been associated with a 55-61% reduction in vertebral fractures (65). Bisphosphonates are also effective in reducing the risk of non-vertebral fractures (OR 0.73, p=0.001) (65). Bisphosphonates are not recommended for use in pregnant or breast feeding women or in severe renal impairment (eGFR < 35 ml/min). They can be associated with gastrointestinal upset, gastritis and gastric ulceration.

Denosumab

Denosumab is the most potent antiresorptive and has been available since 2010. It is administered by subcutaneous injection six monthly and is an monoclonal antibody acting as an antagonist of Receptor Activator of Nuclear factor Kappa-B (RANK) ligand. It has a potent negative effect on bone resorption by preventing binding of RANKL to RANK on mature osteoclasts and their progenitors. It is associated with a 68% relative risk reduction in vertebral fractures at 35 months, 40% hip and 20% other fractures (66). It is unique in that it results in sustained improvement in BMD for up to ten years unlike bisphosphonates where BMD gains plateau at 3-5 years. Its safety profile remains consistent over this time (67). Denosumab is contraindicated in patients with hypocalcaemia and can cause hypocalcaemia, particularly in patients with renal impairment. It may also increase the risk of cellulitis and other infections including ear, nose and throat and gastrointestinal infections (68).

Atypical Fracture and Osteonecrosis of Jaw

There are a number of concerns regarding long term use of these antiresorptive therapies including atypical femoral fracture and osteonecrosis of the jaw (ONJ) which are rare occurrences and likely over emphasised by the media and possibly health professionals in the past (69).

Medication related osteonecrosis of the jaw (MRONJ) is a possible adverse side effect of anti-resorptives, consisting of bone destruction in the jaw including the maxilla and mandible. Patients are affected by MRONJ if they had ongoing or antecedent treatment with antiresorptive drugs (alone or in combination with immune modulators or antiangiogenic medication) and exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region persisting for more than 8 weeks in the absence of radiation therapy or metastatic disease to the jaw (70). A recent review showed an incidence rate for MRONJ of 10/10000 on oral bisphosphonate for less than 4 years, 21/10000 for more than 4 years, 1.7/10000 on zoledronate for 3 years and 4/10000 on denosumab. Incidence for patients on antiresorptive therapies as part of cancer treatment was between 10-190/10000 patients. (71). Other risk factors for MRONJ include use of steroids and dentoalveolar operations including tooth extraction. It is recommended patients attend for regular dental care prior to and during treatment and maintain good oral hygiene. Consideration should also be given to the timing of dental procedures to minimise complications.

Atypical femoral fractures (AFFs) may be a rare adverse effect of bisphosphonates and antiresorptive therapies. They are defined by the diagnostic criteria published by the ASBMR task force(72). Major features include the location of the fracture and that the fracture is associated with no or minimal trauma, is non-comminuted and transverse or short oblique. Although the relative risk of patients with AFFs taking bisphosphonates is high, the absolute risk of AFFs in patients on bisphosphonates is low, ranging from 3.2 to 50 cases per 100,000 person-years. However, long-term

use may be associated with higher risk (~100 per 100,000 person-years). The benefit/AFF risk ratio for 3 to 5 years of BP use in osteoporotic women is overwhelmingly positive: for each AFF caused by BPs, ~1200 fractures, including 135 hip fractures, would be prevented (73). This complication should be considered in patients on treatment reporting thigh or groin pain. Asian race (in North America) and glucocorticoid use are consistent risk factors. In patients with signs of incomplete AFFs, BPs should be discontinued and, in patients with a visible incomplete AFF fracture line, prophylactic surgery can be considered. About 25% are bilateral and imaging of the contralateral femur should be sought following diagnosis (74).

Adherence and persistence

One of the main concerns in prescribing these medications is patient adherence and persistence. A recent Irish study showed that persistence with oral bisphosphonate and denosumab at two years was 49.4% and 53.8% respectively (75).

Selective oestrogen receptor modulator (SERM)

Raloxifene is a SERM that acts as a selective oestrogen agonist and is used in osteoporosis treatment, in particular for younger patients. It has been shown to reduce the risk of vertebral fractures only (30-55% relative risk reduction) (76). The ideal patient for consideration for this medication are younger post-menopausal woman who has no vasomotor symptoms or risk factors for venous thromboembolism.

Hormone Replacement Therapy (HRT)

Hormone Replacement Therapy (HRT) is frequently considered for osteoporosis prevention. HRT consists of hormone replacement to treat symptoms at the time of menopause. It generally consists of oral or transdermal administration of the hormones oestrogen and progesterone. As well as improving symptoms at the time of menopause, it has also been shown to have benefits for bone health. In the WHI studies, there was improved BMD and a lower rate of fractures (HR 0.76 95% CI 0.69-0.83) in women who were treated with HRT (77). However, there are significant risks and adverse effects associated with taking HRT. It is not advised for women with a family history or at increased risk of breast cancer. It is also not recommended if the patient is at risk of thrombotic events or has a history of hypertension or liver disease. HRT has a particular role in the management of women who reach menopause early to prevent excessive bone loss at this time.

Anabolic therapy

Teriparatide is an anabolic agent and is a parathyroid hormone (PTH) analogue. A daily subcutaneous injection provides pulses of exogenous PTH which stimulates osteoblastic more than osteoclastic activity providing a net anabolic effect on bone. Multiple trials have shown significant benefit with vertebral fracture reduction (65% relative risk reduction at 19 months) (78), particularly in patients with previous vertebral fractures and glucocorticoid induced osteoporosis (79). No

primary efficacy end-point data are available for hip fracture but systematic review and meta-analysis level evidence shows OR for hip fracture vs placebo of 0.44 (95% CI 0.22 0.87, p=0.019) (80). Clinical experience with teriparatide is growing and it has now been available for over 20 years with its use expanding to include osteoporosis in men, premenopausal patients, and in combination treatment with denosumab. There is also real world clinical data on its efficacy, predictors of response, adherence and persistence as well as its use in sequential therapy (81). Teriparatide has recently been incorporated into guidelines (IOF, ESCEO, NOGG, SIGN and AACE) as first line therapy in patients at very high risk of fracture (82, 83) (28, 84). This change and the addition of biosimilars to the market will likely lead to increased use. Teriparatide is generally tolerated well. Some side effects include nausea, headache, hypercalciuria, transient hypercalcaemia, dizziness, postural hypotension and leg pain. It is not recommended for use in patients with a history of urolithiasis, severe renal impairment, patients at risk of cutaneous calcification, metabolic bone disease other than osteoporosis and osteogenesis imperfecta, pregnant or lactating women, people who have malignancy involving the skeleton or have had radiation treatment involving the skeleton. (28) Notably, in November 2020, the FDA removed a black box warning regarding the potential risk of osteosarcoma with teriparatide and consideration may be now given now for use more than once (i.e. for more than one 2 year course) (85).

Most recently, romosozumab was approved by the FDA and EMA for the treatment of osteoporosis and is now recommended for use in most clinical guidelines including the recent NOGG guideline in patients at very high risk of fracture (28) This is an antisclerostin monoclonal antibody administered as two subcutaneous injections once monthly for one year. It has both anabolic and antiresorptive effects and is very effective in patients with high fracture risk, relative risk reduction for vertebral fractures of 75% at 12 months (86). A recent study looking at romosozumab vs placebo for 12 months followed by all patients on denosumab for a further twelve months showed the 2-year gains approximating the effect of 7 years of continuous denosumab administration (87). This year Cosman et al published work investigating and confirming the importance of sequence of therapy, showing the benefit of using romosozumab before antiresorptive therapy compared to after (88). Romosozumab does carry a black box warning for cardiovascular risk and it is recommended that it is not used in patients who have had a stroke or myocardial infarction in the year preceding therapy and if such an event occurs on treatment to discontinue treatment (89).

Treatment thresholds

Numerous factors need to be considered in deciding when and what type of treatment to initiate for osteoporosis. Factors related to the patient, and the cause of osteoporosis as well as socio-economic factors must be considered. Importantly, when to start therapy is dependent on the fracture risk and this should be determined on a case by case basis. Recent work has described “imminent fracture risk” and that patients who have recently sustained a fracture (especially in the last 2 years) are at highest risk of future fracture (90). Patients are involved in the decision making process and shared decision making is recommended. Patient adherence is improved by focusing on

patient education and involving the patient in the decision. The concept of fracture risk is central to the establishment of treatment thresholds for osteoporosis (82). The threshold for initiation of osteoporosis treatment after wrist fracture for example varies depending on health care system and cost as well as individual patient and physician factors. No single threshold can be employed universally as reflected in the treatment guidelines.

Fracture risk assessment has become important in the management of osteoporosis (91). Fracture risk is most commonly assessed now using validated risk factor tools such as FRAX, Qfracture and Garvan (92). The most widely used tool is FRAX (93) which is freely available online. Clinicians select their country and input patients age, height, weight, and answer yes or no to a number of risk factors including previous fracture, parent fractured hip, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol 3 or more units/day and if available femoral neck BMD in g/cm2 and the DXA manufacturer as shown in figure 1 above. The tool expresses the outcome of the fracture risk calculation in terms of ten year probability of major osteoporotic fracture (MOF) and hip fracture expressed as a percentage. Adjustments and considerations can be made to the FRAX output for factors such as diabetes mellitus, hip axis length and recurrent falls (28).

Multiple guidelines have been developed in different areas to guide clinicians in the decision to initiate therapy. A systematic review prepared for NOGG and IOF looked at the use of FRAX in 120 guidelines internationally as a tool to assess fracture risk and help determine treatment threshold for patients. Of these, 58 recommended a fixed intervention threshold varying from 4-20% risk of MOF and 1-5% for hip fracture. More than half recommend more than 20% for MOF and 3% for hip fracture though the rationale in most was that this was what was recommended by NOF (National Osteoporosis Foundation) in the US (94). The NOGG guidance in the UK which uses age-dependent thresholds is derived largely from clinical considerations but also takes into account health economics. More recently risk is subdivided into 'high risk' and 'very high risk' for determination of patients suitable for anabolic therapy or for referral to specialist services (95).

In Ireland, osteoporosis guidelines for health professionals were published by the Irish Osteoporosis Society in 2012 (96) and advise not just on pharmacological treatment of osteoporosis but also on general management. The guideline does not recommend the use of a specific fracture risk assessment tools or thresholds. However, the authors do discuss FRAX and it benefits and limitations.

Some guidelines have recently been updated to incorporate romosozumab and anabolic therapy earlier in the treatment algorithm for patients with high fracture risk including the SIGN guidelines (83), IOF-ESCEO position paper (97) NOGG (28), and the AACE/ACE update (84).

Treatment gap

Despite published guidelines in many jurisdictions on pharmacological therapy of osteoporosis, many patients remain untreated. The difference between the people known to require and benefit from treatment and the number receiving treatment is known as the “treatment gap”. This was first noted in the USA. A number of factors are thought to have contributed to the issue including underdiagnosis of osteoporosis. Many patients are not referred or do not present for densitometry as the disease does not have symptoms or cause pain or disability in the absence of fracture. Even in patients who have sustained a fragility fracture, often the fracture is treated but underlying osteoporosis is not diagnosed or treated. Furthermore, in particular in the USA, many patients are hesitant to take medication for osteoporosis. Much of this hesitancy is attributed to media coverage of rare side effects of bisphosphonate medication. In particular, patients are very worried about developing atypical femoral fractures or osteonecrosis of the jaw as these rare potential side effects have been disproportionally covered by media outlets. Despite numerous studies now being available proving the efficacy and safety of these medications, patients are reluctant to take them.

The treatment gap is not just an issue in the USA. Internationally, a gap has been identified between patients eligible for and receiving treatment for osteoporosis A recent study led by Eugene McCluskey looking at primary care in eight European countries (including Ireland) and almost 4000 women over the age of 70 showed that of patients deemed to be at high risk of fragility fracture, 53% were not on treatment for osteoporosis (98). In this study, lack of a documented diagnosis of osteoporosis was a factor contributing to this treatment gap as many patients at high fracture risk are not diagnosed with osteoporosis.

Duration and sequence of treatment

An important concept in management of osteoporosis is that it is a lifelong condition. There is no cure but treatment aims to achieve an acceptable level of risk. Duration and sequence of treatment are important considerations, particularly with regard to timing of different agents. Oral bisphosphonate are generally a first line treatment and should initially be reviewed after 2-3 years of treatment and then at five years with a view to continuation or a 'drug holiday' or change of therapy. Treatment with alendronate can be continued for up to 10 years in high risk patients. Zoledronic acid treatment is typically for 3 years followed by consideration for drug holiday, though therapy can be continued for up to 6 years in some patients. It is preferable to use anabolic agents such as teriparatide or romosozumab first followed by anti-resorptives (88). Cessation of denosumab is associated with rebound in bone loss at the spine and hip and increased vertebral fracture risk (99). Drug switches are not recommended with this medication unless under specialist care (84). Recent NOGG guidelines recommend IV zoledronate to be given six months after the last dose of denosumab with subsequent monitoring of serum CTX to guide timing of further treatment. If this is not possible a further dose of IV zoledronate should be given after a further six months.

Treatment failure should prompt exploration of causes and review of treatment plan. Failure of treatment may be inferred when two or more incident fractures occur while on treatment, failure of suppression of bone turnover markers or continued significant decrease in BMD in a patient treated for more than 12 months with an antiresorptive with no secondary causes of bone loss or fracture and good compliance (100).

1.2.5 Clinical implications of osteoporosis

The clinical outcomes for patients with osteoporosis have been examined in a number of studies. One of the primary outcomes considered is fracture incidence and the resultant morbidity and mortality. Hip fractures are the most studied of the fragility fractures. They are associated with reductions in quality of life, admission to residential care and significant morbidity and mortality. Adverse outcomes are also associated with other fracture types. The outcomes of patients following vertebral fractures and forearm fracture will be explored further below. An evidence base is emerging for outcomes for non-hip and non-vertebral fractures which suggests these are not as benign as initially thought. By initiating treatment for osteoporosis we hope to interrupt the fracture cascade and improve outcomes for patients with osteoporosis.

The Dubbo Osteoporosis Epidemiology Study examined clinical outcomes of patients with osteoporosis over a 25 year period. There is evidence from this study that patients who sustain a fragility fracture are at increased risk of a subsequent fracture soon after the first (imminent fracture risk). The study also showed that hip and vertebral fractures in particular were associated with excess mortality as were all major proximal fractures and distal fractures in older adults over the age of 75. It also showed that this increase in mortality was particularly apparent in those refracturing. Importantly, treatment with bisphosphonates may have mortality benefits though all of the mechanisms are not clear. The authors also found that despite improvements in health and population mortality this excess mortality has not changed on the last two decades (101).

1.2.6 Economic impact of osteoporosis

Osteoporosis and fragility fractures represent a significant economic burden in Ireland and internationally. A report published as part of a compendium for the European Union estimated that approximately 32,000 fragility fracture occurred in Ireland in 2019 representing an increase of 6.1/1000 fractures since 2010. The total direct cost (excluding QALYs lost) amounted to €464.3 million in 2019, €290.8 direct costs of incident fractures, €135.7 long term disability from previous fractures, €27.7 million on assessment and treatment. This accounts for approximately 2.0% of healthcare spending, much lower than the EU27+2 average of 3.5%, suggesting an underinvestment of the healthcare budget in osteoporosis. The monetary value of QALYs lost was reported as €1,456m. (6, 102).

Studies have also assessed the cost effectiveness of treatments for osteoporosis in different countries. ESCEO-IOF developed and published recommendations for the conduct of economic evaluations in osteoporosis (103). Following this, an updated systematic review was conducted of previously performed economic evaluations of osteoporosis medication including sequential therapy (104). This showed that when compared with traditional oral bisphosphonates, 67% of the studies and 82% of the comparisons showed that the alternative drug was cost effective or dominant (at the WTP threshold of 100,000 US dollars). Several drivers of cost-effectiveness were identified including baseline fracture risk, drug effect on the risk of fractures, variations in drug costs, medication adherence or persistence.

1.3 Fragility fractures

Fragility fractures are defined as those that result from mechanical forces that would not ordinarily result in fracture. Other terminology used for these fractures includes low energy fractures and low trauma fractures. The WHO quantified this as forces equivalent to a fall from a standing height or less (105). The most common fragility fractures are of the hip, distal forearm and spine. Hip fractures are associated with increased mortality, morbidity and reduced quality of life (106). In Ireland, the introduction of the Irish Hip Fracture Database and Irish Hip Fracture Standards led to nationwide improvements in service provision and data collection regarding patients with hip fractures. 3487 patients were recorded with hip fractures across 16 hospitals in the Republic of Ireland in 2017 (107) and 3666 in 2020 (108). Similar systems are not consistently in place to evaluate and improve the quality of care provided to patients sustaining other fragility fractures in Ireland (109).

1.3.1 Risk factors for fracture

Many of the risk factors for osteoporosis as discussed previously are also risk factors for fracture. Some of the most often quoted risk factors for fracture include age, gender, family history, presence of a secondary causes of osteoporosis. Other risk factors including those that increase risk of falls are also important. Fracture risk assessment tools may be used to quantify this risk and help in the decision regarding treatment. None of these tools are exact and the recommendations discussed above are largely based on expert consensus with regard to the current evidence.

1.3.2 Fracture Liaison Services (FLS)

FLS is a systematic approach to secondary fracture prevention employed by primary and secondary care institutions globally. The role of the FLS is to evaluate fracture risk in patients who have sustained a fragility fracture and communicate the risk of future fracture and the measures that can be taken to prevent future fracture in these patients. FLS have been shown to improve the level of bone health assessment and treatment and reduce future fracture risk in a structured and cost effective way (110) (111). A recently published systematic review and metanalysis showed that FLS was associated with a significantly lower probability of subsequent fractures and mortality. Reduced mortality was shown in studies comparing outcomes before and after FLS introduction (112).

FLS are organised differently in different institutions. Ganda et al conducted a review of the models of care designed to provide this service and classified them into four types. There are four types of models described.

Type A: FLS identify, investigate and treat patients where indicated.

Type B: FLS identify and investigate only. FLS make recommendations to primary care provider to initiate treatment.

Type C: FLS identify patients and alert the primary care provider that further assessment is needed.

Type D: This model provides osteoporosis education to the fracture patient. The primary care provider is neither alerted nor provided with a recommendation. The more intensive models result in a higher proportion of patients identified and treated for osteoporosis (113).

The first national survey of public hospitals in the Republic of Ireland was conducted recently. It showed FLS to be heterogenous, limited in many cases and poorly supported. A national strategy is currently in development in line with international standards to improve the availability and quality of FLS in Ireland (109).

1.4 Vertebral fractures

A vertebral body fracture associated with low trauma or no trauma is a hallmark of osteoporosis. Vertebral fractures are the most common but arguably the least known about of the osteoporotic fractures. There is no consensus on the exact definition of a vertebral fracture (114). Osteoporotic vertebral fractures often appear as a deformity in the size and shape of the vertebral body sometimes associated with vertebral height loss resulting in a wedge or collapse vertebral deformity. Fractures may also be present without change of vertebral shape or area and may be identified by other methods. In these cases there may be changes consistent with endplate or cortex fracture or other modalities such as MRI may identify the fracture. Studies are limited by differences in diagnostic criteria. Furthermore, the majority of patients (70%) with new vertebral fractures will not present with pain or seek medical attention. However, many studies report the significance of vertebral fractures, in particular, regarding the risk of further fracture and significant morbidity and mortality.

1.4.1 Diagnosis and evaluation

Semiquantitative (SQ) method

The visual SQ method was proposed by Genant et al (115). Using this method a vertebra is graded, from visual assessment of the vertebra by a trained observer, based on anterior height, middle height and posterior height. The fracture is classified based on severity as normal (grade 0), mildly deformed (grade 1, a 20–25% reduction in one of the three heights and a reduction of area 10–20%), moderately deformed (grade 2, a 25–40% reduction in any height and a reduction in area of 20–40%), and severely deformed (grade 3, a 40% or more reduction in height and area). Wang et al provided a modified criteria which can be more useful in clinical settings. If the height loss in a vertebra is more than a third it is severe and if it is less than a fifth it is mild (116).

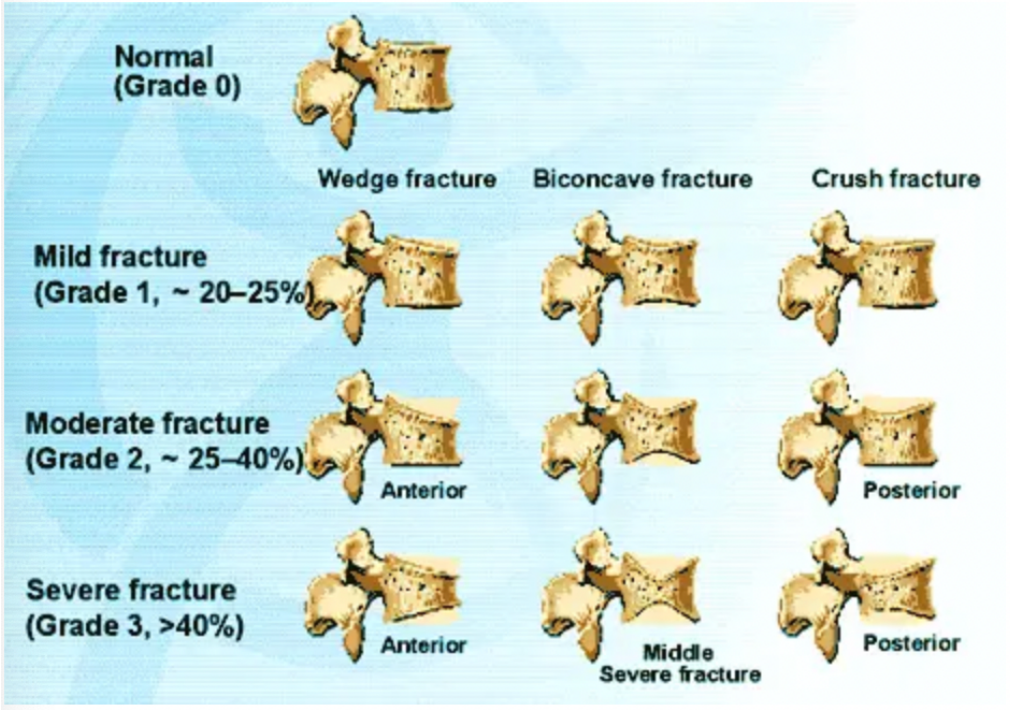


Figure 3 Vertebral Fractures Semi-Quantitative Grading (117)

The SQ method is the basis of much of the current teaching on vertebral fracture identification such as the International Osteoporosis Foundation and the International Society for Clinical Densitometry VFA course. However, there are some limitations of the method. In particular, it is important to bear in mind that not all vertebral deformities detected with this method are true vertebral fractures. Developmental abnormalities or physiologic wedging can sometimes result in false positive reporting of a grade one fracture. Intervertebral disc abnormalities can also lead to apparent vertebral deformities for example Schmorl's nodes or Scheuermann's disease.

Algorithm- based qualitative (ABQ)

Vertebral fractures have radiographic features other than just height loss. A recent review summarised the radiographic morphological signs of osteoporotic VF detectable by an expert reader: (I) anatomic discordance between adjacent vertebrae; (II) loss of parallelism between adjacent end-plates; (III) end-plate disruption as they are impacted into the vertebral body; (IV) fractures of the vertebral anterior cortex or end-plate characterized by cortical discontinuities (ECF); (V) buckling of the vertebral cortex, especially anteriorly (118).

The ABQ method considers vertebral shape abnormalities with a particular focus on the appearance of the endplate not just height loss to identify vertebral fractures. In this way it can improve the specificity for detecting fractures. Some of the features considered using this method are buckling of the cortices and the lack of parallelism of endplates. This method does not include grading fractures severity based on height loss.

Vertebral morphometry

Vertebral morphometry is the identification of vertebral fractures using quantitative measurements of the vertebrae. In recent years a number of studies have been published looking at establishing normative data for comparison purposes though a number of challenges exist including the baseline population to be used.

Role of DXA Vertebral Fracture Assessment (VFA)

The role of VFA was highlighted in a recent position paper published by the IOF (119), highlighting its use in vertebral fracture identification. It reports the change in the estimated fracture risk for patients diagnosed with prevalent vertebral fracture(s) on VFA which may alter treatment decisions. It also highlighted the role of VFA in providing a baseline and therefore allowing accurate monitoring of vertebral fracture for patients on treatment. The review discussed the indications for VFA published by ISCD, IOF-ESCEO and NOF including patients with low bone density, previous fractures or history suggestive of fracture or high fracture risk.

Occult Vertebral Fracture

Some fractures are not detected using standard radiographic techniques. This is particularly common in recent fractures. In some cases the fracture can be visualised on MR or nuclear techniques at an very early stage with the radiographic features following at a later stage.

1.4.3 Incidence and prevalence

The prevalence and incidence of vertebral fractures varies widely. The European Prospective Osteoporosis Study showed the incidence of vertebral fracture in women was 10.7/1000 per year and 5.7/1000 men (120). The European Vertebral Osteoporosis Study showed a 12% prevalence in

men and women in Europe aged between 50 and 79. The prevalence increased in both genders with age though the gradient was steeper with females and there was some geographical variation with the highest prevalence seen in Scandinavia (121). The incidence of vertebral fractures was found to vary from 5% to almost 90% depending on the population and ascertainment technique in a recently published systematic review of Irish osteoporosis vertebral fracture literature. This review included 26 studies (since 2000) and also highlighted the large deficit in studies addressing the epidemiology of vertebral fractures in Ireland (122). Patient characteristics were explored in a another recently published Irish study (123). The group considered 1296 patients attending a FLS and who had VFA. They identified 283 (21.8%) patients with prevalent vertebral fractures. Those with vertebral fractures were older, more likely to be on osteoporosis treatment, have reported height loss, higher FRAX scores and lower BMD at each site. They were also more likely to be on steroids or have secondary osteoporosis. The prevalence in this cohort was three times higher than that known prior to VFA assessment.

1.4.4 Treatment

Treatment of symptomatic vertebral fracture

The treatment options for an osteoporotic vertebral fracture include conservative management, minimally invasive techniques including cementoplasty/percutaneous instrumentation and surgery. Where there are neurological deficits the surgical treatment approaches are clear, though there can be technical challenges in surgical treatment of these fractures due to the osteoporosis itself (124).

Conservative management includes pain management, braces (spinal orthoses), MDT input and are used when the fracture is not displaced and not very painful. The main brace in use is the Thoracolumbar Spinal Orthosis brace (TLSO). Evidence on the efficacy of spinal orthosis for the treatment of vertebral fractures was largely based on non-osteoporotic vertebral fractures in younger adults. Spinal orthosis has certain disadvantages including pressure sores, reduced pulmonary capacity, inadequate mobilisation and weakening of the core musculature. Presently, given the lack of quality evidence, the recommendation for their use remains weak (125). The Royal Osteoporosis Society recently published guidance for the management of symptomatic vertebral fragility fractures which provide excellent guidance on the assessment of patients and pain management (126).

If fracture pain is difficult to control and there are hyperintensities on T2-STIR sequences on MRI (indicating acute oedema), vertebroplasty may be considered. Generally, these techniques are considered to reduce pain during the acute period. However, there is still considerable debate and controversy regarding their effectiveness compared with conservative management (125).

Osteoporosis Therapy for Vertebral Fractures

As previously described, treatments for osteoporosis of the spine are very effective. Teriparatide and romosozumab are now considered first line for treatment of patients at very high risk for vertebral fracture including those with previous fractures. However, romosozumab is currently not available in Ireland. Dual therapy with teriparatide and antiresorptive therapy can also considered for patients at high risk of both hip and vertebral fracture (127).

1.4.5 Outcomes

Clinical vertebral fractures have a similar impact on quality of life (QOL), morbidity and mortality to hip fractures. Some studies report that asymptomatic and clinical vertebral fractures are equally associated with increased risk of further fracture and morbidity (128, 129).

Quality of life

Vertebral fractures can contribute to poorer quality of life for several reasons. In patients who present clinically with an acute fracture there can be significant pain. The fracture can be associated

with functional impairment and loss of independence (130). Patients can require acute hospital admission and intervention or can require increased home supports and are at increased risk hospitalisation following the fracture (131). Multiple vertebral fractures are associated with height loss and change of posture, increased body sway and can contribute to reduction in pulmonary function (132).

Mortality

Studies show that vertebral fractures are associated with premature mortality. Clinically diagnosed vertebral fractures are rarely fatal but studies have shown reduced survival subsequently beyond one year (133). Mortality has been shown to be associated with cardiovascular and pulmonary disease in men and also cancer in women (134) In the Study of Osteoporotic Fractures cohort, women with one of more fractures had a greater age-adjusted mortality rate of 1.23 (95%CI 1.10-1.37) (135). Another prospective study reported increased mortality related to vertebral fractures reaching 28% (v 8%) in patients with ESKD (136).

Risk of subsequent fracture

It is well described that prevalent vertebral fractures on radiographic imaging are predictive for subsequent vertebral fractures (132). Furthermore, the number and severity of the prevalent fractures are associated with an increased risk of further fracture. The "vertebral cascade" is frequently reported where patients are at increased risk of future vertebral fracture within a short timeframe (e.g. more than three in a year). It has also been shown that patients with vertebral fractures are at higher risk of non-vertebral fractures. The higher fracture risk in patients with vertebral fracture remains even after adjustment for age and BMD (137).

1.5 Wrist fractures

1.5.1 Incidence

Distal forearm fractures are common with many studies investigating their incidence. The European Prospective Osteoporosis Study (EPOS) investigating limb fractures across Europe showed the highest incidence of distal forearm fracture in Scandinavia and Eastern Europe (138). A study in southern Sweden in 2001 reported that the overall incidence of distal radius fracture during 2001 was 26 (95% CI 23–29) per 10,000 person-years. Below the age of 50 years, the incidence was approximately 9 per 10,000 person-years irrespective of gender. Among women the incidence increased sharply from the age of 50 years and almost doubled with each 10-year age interval up to the age of 70 years and peaking at the age of 90 years to 144 per 10,000 person-years (139). A study performed in the UK found the age-adjusted incidence for 35 years and over was 36.8/10 000 person-years in women and 9.0/10 000 person-years in men (140). Multiple studies have shown an increase in incidence of distal forearm fractures in recent decades (141, 142). It is thought that the reason wrist fracture incidence plateaus in older old age is due at least in part to the injury being caused usually by falling on the outstretched hand which due to changes in mobility, reflexes, onset of dementia and possibly other reasons is less likely in this group.

Risk factors

A number of risk factors are associated with distal forearm fracture, including primarily femoral neck BMD, distal forearm BMD, dietary calcium, height loss, and recurrent falls (143) (144) (145). Higher incidence of forearm fractures has also been seen in urban rather than rural women (146). Biomechanical properties of the radius have also been explored as risk factors for fracture. Melton et al published a study highlighting not only the importance of BMD at the femoral neck and distal radius but also geometry, microstructure and strength of the distal radius (147). Vitamin D deficiency has been shown to be associated with distal forearm fractures in a number of studies. (148) (149) (150) though results are inconsistent (151). Obesity has been shown to be associated with a decreased incidence of wrist fractures (152), however it is associated with more complex injuries when they do occur (153). Studies suggest that further research is needed in establishing the determinants and risk factors for forearm fractures (154). Further clarity on these risk factors may help inform policy and define preventive strategies.

Sarcopenia

Sarcopenia is a muscle disease (muscle failure) rooted in adverse muscle changes that accrue across a lifetime. There has been some discussion surrounding the definition and diagnostic criteria in recent years. In 2018, an operational definition of sarcopenia with three criteria was agreed: 1. Low muscle strength, 2. Low muscle quantity or quality, 3. Low physical performance. Probable sarcopenia is identified by the first criterion. Diagnosis is confirmed by addition of criterion 2 and if

all three are met sarcopenia is considered severe (155). Sarcopenia can be considered primary or secondary and acute or chronic. A number of different causes include aging, disease (inflammatory conditions, malignancy, osteoarthritis, neurological disorders), inactivity and malnutrition. Osteosarcopenia is increasingly recognised as the presence of osteopenia/osteoporosis and sarcopenia. It is anticipated that diagnosis and treatment for osteosarcopenia will become part of more routine healthcare in the future with more attention given in comprehensive geriatric assessment to the treatment of coexisting sarcopenia in patients presenting with osteoporosis/fragility fractures (156). Studies have shown a higher proportion of patients with wrist fracture have sarcopenia than age matched controls who have not sustained a fracture. Studies have also shown similar radiographic outcomes but poorer functional outcomes (157).

Osteoporosis prevalence

The majority of distal forearm fractures in patients over the age of 50 are fragility fractures. A Dublin study showed 68% of patients presenting with distal forearm fractures had T scores in the osteoporotic range at the hip or spine (158). A similar study in Northern Ireland found that 45% of patients presenting with distal forearm fracture were osteoporotic on at least one site on a DXA at either the hip, the spine or the distal forearm (159). Almost half (45.1%) of patients with a distal forearm fracture in a Korean study had osteoporosis when evaluating the AP spine on a DXA scan (160). Kanterewicz et al showed that 70% of patients with a Colles fracture had low BMD (161) while 39% in a Nottingham study (NOCOS) were diagnosed with osteoporosis (162) and 59% in a more recent study in Malaysia (163). An older study examined the differences in BMD measurements at the spine and UD forearm in patients with vertebral fractures, wrist fracture, both and controls showing that BMD was lower at the site that fractured and in patients with both fractures, BMD was similarly low at both the LS spine and UDR (164).

Table 1: Proportion of patients diagnosed with osteoporosis following wrist fracture

Author (year of publication)	Number	Mean age (years)	Proportion with osteoporosis	Proportion with low Bone Mineral Density	Comment
Earnshaw (1998) (165)	106	65.7	50%		<65: LS 17%, Hip 24%; >66: LS 24%, Hip 55%
Kanterewicz et al (2002)	58		Wrist 60%, LS 47%, Hip 19%		
Hegeman et al (2004)	94	69	51%	85%	Aged <65:LS -1.41±1.49, Hip -1.17 ±1 Aged >66: LS -2.16±1.53, Hip -1.75 ±0.92
Beringer et al (2005)	375		45%		
Lofman et al (2007)	171	67	37%	52%	Hip: 50-59 19%, 60-69 15%, 70-79 83%
Bahari et al (2007)	100	67.8	68%	28%	
Lashin and Davie (2008)	186	65.5	33.9%		Hip: 50-64 31.1%, 65-74 34.3%, >75 40%
Lee et al (2010)	54	64	57.4%		LS: 50-59 38%, 60-69 34%, 70-79 67%
Mellon et al (2010)	100	62			FN: 0.81±0.11; LS: 1.02±17
Oyen et al (2011)	749	66	Women 34%; Men 17%		
Jang et al (2012)	104	65			FN BMD: DRF 0.65±0.16, Control 0.7±0.14
Massey et al (2015)	128		Aged :35-50: LS 17%, Hip 6% Aged >50: LS 26%, Hip 27%	Aged: 35-50: LS 23%, Hip 43% Aged >50: LS 27% Hip 48%	
Jung et al (2016)	206		51.5%		
Niempoog et al (2019)	100		59.5%	29.1%	

1.5.2 Treatment

Diagnosis and treatment of osteoporosis in patients with fragility fracture has recently been coordinated via Fracture Liaison Services in many countries. Many studies have identified that despite distal forearm fractures being associated with a high incidence of osteoporosis and future fracture risk, many patients at the time of presentation and diagnosis do not receive a bone health assessment (166, 167).

Surgical treatment

There are many controversies in the surgical treatment of distal forearm fractures. These include how to best classify a fracture and what approach should be taken to guide optimal treatment (168). There are several classification systems for distal forearm fractures and these have been examined in many studies and include: clinical, conventional radiology and more recently CT imaging (169). The first description of distal forearm fractures was attributed to Abraham Colles an Irish surgeon and graduate of Trinity College Dublin (170). Since then, many attempts were made to further classify these fractures. A number of other systems have developed using conventional radiology including Melone's classification which focuses on the intra-articular fracture of the distal radius, and in particular the importance of the medial complex. A recent review summarized the four other most common classification systems: Frykman (171), Fernández (172), Universal (173), and AO classification systems (174). Table 2 summarises the radiographic features of each classification system (169).

Table 2: Classification, types, and descriptions of distal forearm fractures.

Frykman (1967) I-VIII	
I	Extra-articular
II	Extra-articular with ulnar fracture
III	Intra-articular into radiocarpal joint
IV	Intra-articular into radiocarpal joint with ulnar fracture
V	Intra-articular in radioulnar joint
VI	Intra-articular into radioulnar joint with ulnar fracture
VII	Intra-articular into radiocarpal + radioulnar joints
VIII	Intra-articular into radiocarpal + radioulnar joints with ulnar fracture
Fernández (2001) 5 types, based on trauma mechanism	
Type 1	Bending fracture of metaphysis
Type 2	Sheering fracture of joint surfaces
Type 3	Compression fracture of joint surface
Type 4	Avulsion fracture or radiocarpal fracture-dislocation
Type 5	Combined fracture associated with high high-velocity injuries
Universal (1993) 4 types, subdivision in 2 x 3 groups	
Type 1	Extra-articular fracture, without deviation
Type 2	Extra-articular fracture with deviation
2A	Reducible and stable
2B	Reducible and unstable
2C	Irreducible
Type 3	Intra-articular fracture, without deviation
Type 4	Intra-articular fracture, with deviation
4A	Reducible and stable
4B	Reducible and unstable
4C	Irreducible
AO/ASIF (2007) 3 types, 9 groups	
A	Extra-articular fractures
A1	Ulnar fracture, radius intact
A2	Radius fracture, simple and impacted
A3	Radius fracture. multi-fragmentary
B	Partial articular fracture
B1	Radius fracture, sagittal
B2	Radius fracture. frontal, dorsal rim
B3	Radius fracture, frontal, volar rim
C	Complete articular fractures
C1	Articular simple + metaphyseal simple
C2	Articular simple metaphyseal multi-fragmentary
C3	Articular multi-fragmentary

However, it is important to note that older adults have been observed to tolerate poorer radiological outcomes rather well (175). This review and another recent systematic review found no difference in outcomes between different surgical techniques (176). In general, non-operative treatment can be considered to be the gold standard but shared decision-making between the patient and the treating physician is important.

Blue book standards for treatment

The British Orthopaedic Association and the British Society for Surgery of the Hand collaborated to publish the Blue Book: Best Practice for Management for Distal Radial Fractures in 2018 (177). This guideline summarised the available literature in many of the controversial areas of management of distal forearm fractures. The standards highlight a number of areas where further research is needed in the management of distal forearm fractures. However, compliance with these standards has not been examined in an Irish context.

The Blue Book guidelines highlights that in patients aged over 65 with moderately displaced fractures, manipulation may not improve outcome, and that immobilisation can be achieved using either full cast or back slab. In patients over 65, non-operative treatment can also be considered as primary intervention for displaced distal radius fractures (DRFs). However, they state other factors such as pre injury function, medical comorbidities, and fracture characteristics should be considered. Surgical options include manipulation under anaesthesia with K-wires (dorsally displaced DRFs), and open reduction and internal fixation (those that require open reduction or those with an intra-articular step or gap). Internal fixation has been found to be superior to external fixation with better early functional outcomes and lower risk of complications.

The Blue Book also discusses rehabilitation. Rehabilitation of this injury is generally divided into three stages, immobilisation, mobilisation and strengthening. They report that there is insufficient evidence for or against any form of rehabilitation whilst the patient is being managed with immobilisation or after removal of cast for patients managed nonoperatively. There was no evidence on the effect of rehabilitation provision on patient outcomes following surgery compared to no rehabilitation. There was insufficient evidence that physiotherapy or occupational therapy is more likely to restore function versus a home exercise group programme in those with uncomplicated DRFs, nor is there sufficient evidence for one rehabilitation intervention over another.

1.5.3 Outcomes

Patient Reported Outcome Measures (PROMs) are questionnaires used to elicit information from patients. A recent research gap analysis identified a gap in the evidence regarding outcomes in older trauma patients. This study supports an emphasis on patient-reported measures (178). Assessing outcomes in this way has become increasing relevant and useful in capturing self-reported outcome in the setting of adult patients with distal forearm fractures. Generic instruments like the short form 12 (SF12) and short form 36 (SF36) can measure the impact of various conditions on health status (179). They are useful in that they allow comparison of health impact across a number of conditions. A limitation of these instruments is their failure to capture condition specific functional outcomes.

Region specific PROMs

A number of measures are used both in research and in clinical practice; Patient Rated Wrist Evaluation (PRWE) (180), Disability of the Arm Shoulder and Hand Outcome Measure (DASH) (181), Patient Evaluation Measure (PEM) (182), Michigan Hand Questionnaire (MHQ) (183), Brief MHQ. The Distal Radius Working Group of the international Society for Fracture Repair and the International Osteoporosis Foundation reported recommendations for the evaluation of outcomes (184). They suggested the core outcomes to be measured were pain and function as well as a measure of treatment complications. Pain frequency and intensity should be assessed as in the pain section of the PRWE or using a Visual Analogue Scale. It is recommended that function is best assessed using PRWE or DASH. The Blue Book (177) concluded that there is insufficient evidence to recommend one optimal PROM in the setting of DRFs, however pending future research an interim recommendation was made for the use of either PRWE or DASH based on available evidence for responsiveness in this setting (180). There is also no Irish study looking at PROMs in patients following distal forearm fracture.

Studies have examined the impact of distal forearm fracture on function and quality of life using PROMs and other assessments. A review published in 2022 included 78 studies (n = 688,041 patients) and concluded that a high proportion of people aged over 50 years with wrist fracture experience pain and functional limitation more than 6 months after fracture with associated increased healthcare costs and impact of quality of life (185). At six months, there is evidence of reduced quality of life and functionality (186). Furthermore, there is also small number of studies examining longer term outcomes showing continued reduction in quality of life (187).

Age and income have been shown to be associated with poorer outcome (188) Acute fracture management may also have an impact. An Irish study examining patient outcomes following the use of a splint versus cast (in minimally displaced wrist fractures), showed that the removable splint was better (189). Acceptable radiographic reduction was not associated with patient reported outcomes in older adults treated conservatively (190). A recent study showed that patients who had a fracture that could be treated non-surgically had less pain and better outcomes than those treated surgically

(191). Similar results were seen in some smaller studies with follow up periods of 2-3 years (192, 193).

Surgical complications have been described as a potential cause of poorer outcomes in the surgical candidates (194) and include nerve compression (median, radial, ulnar, reflex sympathetic dystrophy), bone/joint complications (arthritis, carpal instability, delayed union, distal radioulnar joint problems), tendon complications (dupuytren's contracture, tendon adhesions/scarring, tendon rupture/tear, tendonitis/tenosynovitis, trigger finger), compartment syndrome, and pin-site/incision infection.

Grip strength

Grip strength measurements have been studied extensively in older adults. Studies have identified associations with BMD, fracture incidence, falls, depression, and multimorbidity as well as cognitive performance, hospitalisation and mortality (195). In the context of wrist fractures, clinically significant differences have been shown between grip strength in the injured hand versus the uninjured hand in the in the first six months after injury. By two years, the difference is minimal (196).

Range of Motion (ROM) at joint

Range of motion at the wrist is often used as an outcome measure. Several studies have investigated the link between wrist ROM and function or patient reported outcomes but have not found an association. However, early digit mobilisation may be associated with patient satisfaction (197).

Radiographic features

Multiple studies have examined radiographic features of wrist fractures and outcome. A recent systematic review and meta-analysis explored the relationship between radiological parameters and patient reported outcomes. Sixteen articles were included comprising 1961 patients with DRF. A significant difference of 4.35 points in PROM was found in favour of an acceptable radiological reduction. Dorsal angulation and ulnar variances were also shown to be associated with significant improvements in PROMs. The mean difference in each association did not meet the thresholds of the minimally clinically important difference and were deemed unlikely to be clinically important (198).

Hospital admission and health care use

Hospital admission and health care use are costly consequences of distal forearm fracture. A study in central Finland showed an admission rate of 9% (199). An Italian study showed rates of 12% in women and 14% in men (200). However, an Australian study showed that 26.2–28.9% of patients presenting to ED with wrist fracture required hospital admission. This number was higher for older patients and women (201). A French study showed that mean length of stay and also the cost of stay

increased with age. The average cost of an admission following wrist fracture was estimated at €2100 (202). Evidence from the US Medicare system showed an increase of 19.5% in admission rates in the 6 months after a wrist fracture. They also reported an increase in all forms of post-acute care after fracture including inpatient care (13.1% increase) and home health care (12.1% increase) (203). A recent Irish study analysing emerging trends for hospitalisation following fragility fractures showed that distal forearm fractures accounted for approximately 2000 admissions and 12,000 acute care bed days a year. There was also an increase of 6% in the number of patients admitted following wrist fracture and a respective 87% and 10% increase in the number of male and female acute care bed days used between 2004 to 2014 (204).

Mortality

One year mortality rates for patients post wrist fracture are inconsistent. Most studies suggest the mortality is the same as the general population ranging from 2-6% (205) (206) (207) (208), with others showing excess mortality (203) (209). These differences are largely accounted for by differences in study design, age and frailty of the patients.

Risk of subsequent fracture

Distal forearm fracture has been shown to be associated with a 2-3 times increased risk of subsequent hip fracture. A review published in 2000 calculated the pooled relative risk of future fracture following distal forearm fracture as 2.0 (1.7- 2.4) (3.3 (2.0 -5.3) for wrist, 1.7 (1.4 -2.1) for vertebral, 1.9 (1.6 -2.2) for hip and 2.4 (1.7, 3.4) for all non vertebral (210). A post hoc analysis of the Women's Health Initiative study showed an increased risk of subsequent fracture in women with a history of wrist fracture, who were followed up for a mean of 11.8 years. Overall, 15.5% subsequently experienced a non-wrist fracture which was independent of BMD (211). Similar rates of hip fracture have been identified in other studies of females post wrist fracture (212). Cuddihy et al showed, the cumulative incidence of any subsequent fracture was 55% by 10 years and, 80% by 20 years, following the initial distal forearm fracture. They also showed an increased risk of vertebral fractures in all age categories and hip fracture in women who sustained a wrist fracture after, but not before, the age of 70 (213). However, most other studies show an increased rate of hip fractures at all ages post wrist fractures (214, 215).

1.6 Study aim

This research thesis comprises four main study aims as outlined below:

(a) To examine the characteristics of patients who have sustained low trauma wrist fractures

(b) To examine the characteristics of patients with vertebral fractures

(c) To investigate characteristics in a prospective cohort of patients following a low trauma distal forearm fracture

(d) To assess outcomes in the above prospective cohort and to study the factors related to these outcomes.

Chapter 2: Characteristics of patients attending BHC with previous wrist fracture

2.1 Introduction

Distal forearm or wrist fractures are a very common fracture and can account for up to 18% of all fractures in patients over the age of 65. Despite this, studies investigating the characteristics of these patients and in particular their bone health status are limited, and sample sizes are small.

Any fragility fracture, including a wrist fracture, increases the risk of subsequent fracture. When a patient has a wrist fracture from a low energy trauma, it is an opportunity to assess fracture risk and evaluate the need for anti-osteoporosis treatment. Research in recent years has looked at the characteristics of patients with wrist fractures and assessed whether it is a "signal fracture" that may indicate high risk of future fracture as reported in Chapter one.

The aim of this study was to identify the characteristics of patients attending a bone health clinic who had sustained a wrist fracture. In particular, we aimed to explore demographic characteristics, as well as parameters of bone health including areal BMD (as measured by DXA), calcaneal QUS and laboratory results including serum vitamin D status (25(OH)D) and bone turnover markers (BTM). We also aimed to establish the point prevalence of osteoporosis/osteopaenia using standard DXA criteria and examine if patients with osteoporosis had previously been prescribed antiosteoporosis medication.

2.2 Methods and materials

2.2.1 Study population

Patients were referred to the service from the inpatient fracture liaison service (FLS). We also see patients who are referred for osteoporosis and bone health management from other hospital services and general practitioners, some of whom may have wrist fractures. Data regarding all patients seen in the service are recorded in the Bone Health and Osteoporosis Service database. Patients were included in the study if they had a fragility wrist fracture and were aged over 18 years.

2.2.2 Data collection

This database was completed prospectively at the time the patient was assessed in the nurse led clinic by the clinical nurse specialist. Data were compiled regarding demographic features including age, sex and medical history. Previous medical diagnoses were documented as reported by the patient and as outlined in the patient chart or referral letter. Medications were reported by the patient and clarification was sought from their pharmacist where necessary. Previous bone health diagnosis was recorded as well as any bone health treatment being taken at the time of assessment including calcium, vitamin D, antiresorptives or anabolic therapy.. All patients were asked about previous fracture and where possible fracture history was confirmed by referring to radiology results or the patient hospital record where available.

Biophysical measures

Weight and height

Weight was measured with a calibrated scale accurate to 0.1kg. Height was recorded using a stadiometer to the nearest 0.01m. Body mass index (BMI) was calculated as per the standard definition (weight/height^2). Measurements were obtained prior to assessment with DXA.

Heel Ultrasound (QUS)

We used the Achilles Insight (General Electric) for our calcaneal quantitative ultrasound assessment. Ultrasound waves pass through the centre of the heel. There are two transducers as part of the system, one transmitting and one receiving. The acoustic coupling between the two transducers is obtained by placing gel between the heel and two membranes containing water at a temperature of 35C. The right heel was assessed for each patient by placing It between the two membranes. The quantitative ultrasound output measures are Speed of Sound (SOS) and Broadband Ultrasound Attenuation (BUA). The device uses these to calculate a stiffness index and T score. The T score was used for our results. Quality control was conducted before each test as per manufacturer's specifications.

DXA

BMD was determined by a Lunar Prodigy DXA system (Lunar Corp., Madison, WI) until 2015 whereas an Hologic Horizon A scanner was used thereafter, with the same NHANES III reference population used for both. The DXA scans were obtained by standard procedures supplied by the manufacturer. Daily quality control was carried out by measurement of a lunar phantom. All scans were performed by trained radiographers. The outcome variables recorded were areal BMD (g/cm2) and T score at hip, spine or distal third forearm. Forearm sites were assessed if there is a specific indication (hyperparathyroidism) or if other sites of assessment are unavailable.

Blood tests

Vitamin D and serum BTM

Vitamin D (25(OH)D) and parathyroid hormone (PTH), CTX, Osteocalcin, PINP and total Alkaline Phosphatase (ALP) were measured. Morning blood samples for 25(OH)D and BTMs were taken on the day of assessment, and centrifuged within two hours. Samples were stored at -20°C and batched for later analysis at the biochemistry laboratory. The laboratory at SJH is a participant of the Vitamin D External Quality Assessment Scheme (DEQAS). 25(OH)D were measured by liquid chromatography mass spectroscopy (LCMS) using a standardised assay (Mass Chrom) and National Institute of Standards and Technology (NIST) vitamin D standard reference material. The inter and intra-assay coefficient of variation were 5.7% and 4.5%.

Other blood tests

Other blood tests were also performed including Full Blood Count. (FBC), renal, liver and bone profiles, serum protein electrophoresis, thyroid function tests, coeliac screen according to standard laboratory procedures. Haemoglobin results are categorised by the presence of anaemia; haemoglobin for females less than 11.5 g/dl and for males less than 13.5g/dl.

2.2.3 Statistical analysis

Data collected between December 2004 and January 2019 were analysed. Data was exported to Excel, cleaned and coded and then exported to SPSSv26 for analysis. Means and standard deviations were used for normally distributed variables or otherwise medians and interquartile range. Patients were categorised by BMD diagnosis (normal, osteopaenia or osteoporosis) and separately by sex. One way anova and chi square tests were used as appropriate to compare differences in characteristics. Predictors of BMD at each site were assessed applying normal criteria including non-collinearity and normal distribution of variables, Finally, we categorised the population into those on or not on anti-osteoporosis treatment and compared for any differences.

2.3 Results

2.3.1 Patient inclusion

We identified 1724 patients who sustained a wrist fracture and attended our service between December 2003 and January 2019. The graph below shows the variation in the number of people recorded each year with wrist fractures.

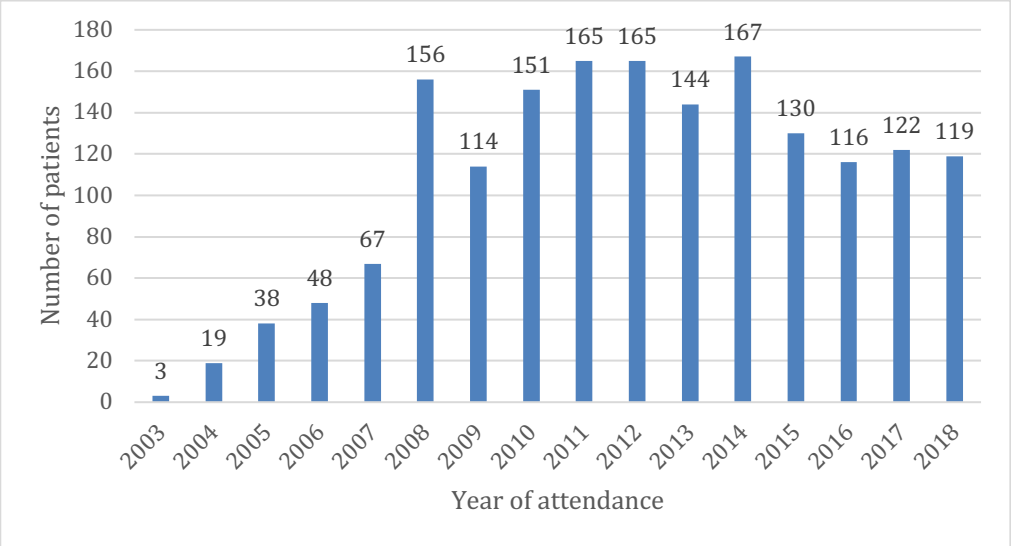


Figure 4: Number of cases recorded each year 2003-2019

The initial increase in the number of cases each year may reflect the fact that the database was only established in 2003 and gradually incorporated into practice. There were only 3 cases captured in 2003, though data collection only began in December of that year. However, .the number recorded between 2008 and 2014 was relatively constant followed by a slight reduction from 2014 to 2018 with an average of 140 patients each year during this period.

2.3.2 Patient characteristics

Table 3: Characteristics of patients with wrist fractures (2003-2019)

Patient characteristics (n)	**Number (%)**
Sex (1724)	
Female	1492 (86.5%)
Male	232 (13.5%)
Age, years (1724)	Mean 67.8±13.1
<50	121 (7.0%)
50-59	327 (19.0%)
60-69	449 (26.1%)
70-79	485 (28.1%)
80 and older	342 (19.8%)
Fracture history (1724)	
Vertebral fracture	426 (24.7%)
Hip fracture	263 (15.2%)
Body Mass Index (1342)	Mean 25.7 ±5.0
Underweight (< 18.5 kg/m2)	75 (5.6%)
Normal (18.5-24.9 kg/m2)	582 (43.4%)
Overweight (25.0-29.9 kg/m2)	448 (33.4%)
Obese (>30.0 kg/m2)	237 (17.7%)
Medication history (1666)	
>5 regular medications	600 (36%)
Anti-resorptive treatment	624 (37.5%)
DXA diagnosis (1669)	
Normal	148 (8.9%))
Osteopaenia	554 (33.2%)
Osteoporosis	967 (57.9%)
Spine T score (1622)	Mean -2.3 ±1.4
>-1.0	293 (18.1%)
-1 to < -2.5	496 (30.6%)
< -2.5	833 (51.3%)
Femoral neck T score (1081)	Mean -1.7±1.0
>-1.0	230 (21.3%)
-1 to < -2.5	572 (52.9%)
< -2.5	279 (25.8%)
Total hip T score (1244)	Mean -1.8 ±1.1
>-1.0	281 (22.6%)
-1 to < -2.5	576 (46.3%)
< -2.5	387 (31.1%)
Forearm T score (112)	Mean 3.1±1.7
>-1.0	17 (15.2%)
-1 to < -2.5	18 (16.1%)
< -2.5	77 (68.7%)
US heel T score (1090)	Mean -2.2 ±1.3
>-1.0	191 (17.5%)
-1 to < -2.5	407 (37.3%)
< -2.5	492 (45.1%)

Table 4: Characteristics of patients with wrist fractures attending (2003-2019 (continued)

Patient characteristics (n)	**Number (%)**
Anaemia (907)	
Male	31 (3.1%)
Female	168 (21%)
CKD stage* (954)	
I	383 (41%)
II	391 (41.9%))
III	151 (16.2%)
IV	8 (.9%)
V	1 (.1%)
Vitamin D, nmol/l (1031)	
<30	127 (12.3%)
30-49.9	180 (17.5%)
>50	724 (70.2%)
PTH, pg/ml (896)	
>65	103 (11.5%)
Serum Calcium, mmol/l (886)	2.33 ± 132
Phosphate, mmol/l (917)	1.03 ± 18
BTM (844)	
ALP (IU/L)	83.5±38
CTX (ng/ml)	0.316±.22
Osteocalcin (ng/ml)	23±13.5
PINP (ng/ml)	48±35

*PTH: Parathyroid Hormone, ALP: alkaline phosphatase, CTX: C terminal telopeptide of type 1 collagen, P1NP: N terminal propeptide of type 1 procollagen, Hb: Haemoglobin, Cr: Creatinine , *CKD stage calculated using MDRD*

Demographics

There were 1724 patients, 86.5% were female and mean age was 67.8±13.1years and ranged from 17-100 yrs. The number on which other characteristics were reported varied. BMI was available for 1342 patients and mean was 25.7 +/-5.0 and ranged between 13.4 and 49.6 kg/m2. Overall, 5.6% were underweight, 43.4% had normal BMI, 33.4% were overweight and 17.7% were obese.

Medications

Of 1666 patients representing 96.6% of the cohort, 37.5% were on prescribed antiosteoporosis medication. On further analysis of this group, all patients were taking antiresorptive therapy. About one third (36%) had polypharmacy (were taking more than five regular medications).

DXA & QUS heel result & fracture prevalence

Data for BMD for hip or spine were available on 96.8% (1669/1724) of the cohort. Based on central DXA (hip or spine scores), 57.9% had osteoporosis, 33.2% osteopaenia and 8.9% normal bone density.

When subcategorised by site, 51.3% had osteoporosis in the spine, 31.3% at the total hip and 25.8% at neck of femur. However, normal BMD occurred in 18.1% in spine, 22.6% at total hip and 25.8% at neck of femur. The number of patients who had DXA at the forearm was much lower (n= 1120) with 68.7% having T scores <-2.5, 16.1% between -1.0 to <-2.5 and 15.2% in the normal range. On QUS 47.5% had a T scores <-2.5 and 37.3% between -1.0 to <-2.5. From the entire cohort (n=1724), about one quarter (25.4%) had a history of vertebral fracture and 15.2% a hip fracture. These patients were significantly more likely to have osteoporosis on DXA than those with only wrist fractures (P=0.002) . Patients who also had a vertebral or hip fracture were also more likely to be older (mean age 72.5 vs 66.3 years, P=0.000). and (74.9 v 66.5 years, p=0.000) respectively.

Blood test results

There was evidence of anaemia in 3.1% of males and 21% of females for whom full blood count results were available (n=907). 17.2% (160/954) had evidence of CKD stage IIIa or higher. 70.2% (724/1031) of those with vitamin D results had replete status (> 50nmol/) and in a smaller sample size, 11.5% (103/896) had biochemical evidence of hyperparathyroidism.

BTM results were available for 49% (844/1724) of the cohort. Mean values for ALP were 83.5 ± 38.0 (normal range 35-104 IU/L), CTX: 0.316±0.220 (premenopausal range 0.016-0.573 ng/ml), osteocalcin: 23.0±13.5 (range 13-48 ng/ml), and PINP was 48.0±35.0 (range 15.1-58.6 ng/ml)

2.3.3 Patient characteristics categorised by DXA diagnosis

Table 5: Patient characteristics categorised by DXA diagnosis

Patient characteristics	Normal	Osteopaenia	Osteoporosis	P-value°
Female (1669)	109 (73.6%)	474 (85.6%)	859 (88.8%)	0.000
Age group (1669)				
<50	14 (9.5%)	43 (7.8%)	60 (6.2%)	0.000
50-59	40 (27.0%)	125 (22.6%)	158 (16.3%)	
60-69	41 (27.7%)	160 (28.9%)	235 (24.3%)	
70-79	32 (21.6%)	143 (25.8%)	293 (30.3%)	
80 and older	21 (14.2%)	83 (15.0%)	221 (22.9%)	
Fracture history (1669)				
Vertebral fracture	20 (13.7%)	134 (24.2%)	261 (27.0%)	0.002
Hip fracture	14 (9.7%)	62 (11.4%)	171 (17.8%)	0.001
BMI (1326)				
Underweight (<18.5%)	1 (0.9%)	5 (1.1%)	69 (8.9%)	0.000
Normal (18.5-25))	28 (24.3%)	150 (34.3%)	397 (51.2%)	
Overweight (25-30)	42 (36.5%)	175 (40.0%)	228 (29.4%)	
Obese (>30)	44 (38.3%)	107 (24.5%)	82 (10.6%)	
Polypharmacy (1615)	58 (46.8%)	182 (31.3%)	343 (36.7%)	0.304
Osteoporosis treatment (1615)	18 (12.8%)	147 (27.8%)	435 (48.3%)	0.000
QUS heel T score (1074)				
>-1	46 (51.7%)	88 (25.2%)	54 (8.5%)	0.000
-1—2.5	30 (33.7%)	158 (45.3%)	216(34%)	
<-2.5	13 (14.6%)	103 (29.5%)	366 (57.5%)	
CKD *(907)				
I	16 (35.6%)	76 (36.7%)	280 (42.8%)	0.010
II	17 (37.8%)	95 (45.9%)	266 (40.7%)	
III	9 (20%)	35 (16.9%)	104(15.9%)	
IV/V	3 (6.7%)	1 (0.5%)	4 (0.6%)	
BTM				
Alkaline phosphatase (IU/L)	83.87±41.2	77.83 ± 28.6	85.11±39.6	0.054
CTX (ng/ml)	0.279±0.21	0.290± 0.19	0.33±0.24	0.033
CTX <0.300	28 (5.7%)	119 (24.0%)	348 (79.3%)	0.275
Osteocalcin (ng/ml)	20.86±10.2	22.17±12.6	23.80±14.5	0.181
PINP (ng/ml)	45±23.2	49.26±39.8	49.69±36.6	0.746
Vitamin D (nmol/l) (1006)	69.3±32.8	69.1±28.5	66.7±31.4	0.445
<30	6 (6.3%)	22 (23.2%)	67 (70.5%)	0.417
30-49.9	15 (7.4%)	53 (26.1%)	135 (66.5%)	
>50	52 (7.3%)	218 (30.8%)	438 (61.9%)	

*DXA: Dual-energy X-ray Absorptiometry, BMI: Body mass index, QUS Quantitative ultrasound BTM: Bone turnover markers, PTH: Parathyroid Hormone, ALP: alkaline phosphatase, CTX: C terminal telopeptide of type 1 collagen, P1NP: N terminal propeptide of type 1 procollagen, Hb: Haemoglobin, Cr: Creatinine °P value refers to analysis of all three categories using chi square test *CKD stage calculated using MDRD*

There was an increasing proportion of females when moving from a diagnosis of normal BMD to osteoporosis. Male patients with osteoporosis or osteopenia were more likely to have anaemia (p=0.013) and patients with normal BMD were less likely to have advanced kidney dysfunction (CKD stage IV/V) (p=0.010). There was a higher proportion with a central DXA diagnosis of osteoporosis with increasing age, ranging from 48.9% in those aged 50-59 to 68.0% when aged >80 years. See also figure 5 below. Higher prevalence of obesity was identified in those with normal BMD (38.3%) versus osteopaenia (24.6%) or osteoporosis (10.6%) (P=0.000) Patients with osteopenia or osteoporosis on DXA were also more likely to have sustained either vertebral (p=0.002) or hip (p=0.001) fractures. In fact, over a quarter (27%) with osteoporosis had a history of a vertebral and 17.8% a hip fracture. Those with osteoporosis were also more likely to have been on treatment with anti-osteoporosis drugs (p<0.001) though this still only occurred in less than half 48.3% of these patients. There was no significant difference in rates of polypharmacy between the groups. Patients with osteoporosis by DXA criteria as expected were more likely to have osteoporosis on Calcaneal QUS (p<0.001). Mean difference in vitamin D levels by DXA diagnoses.

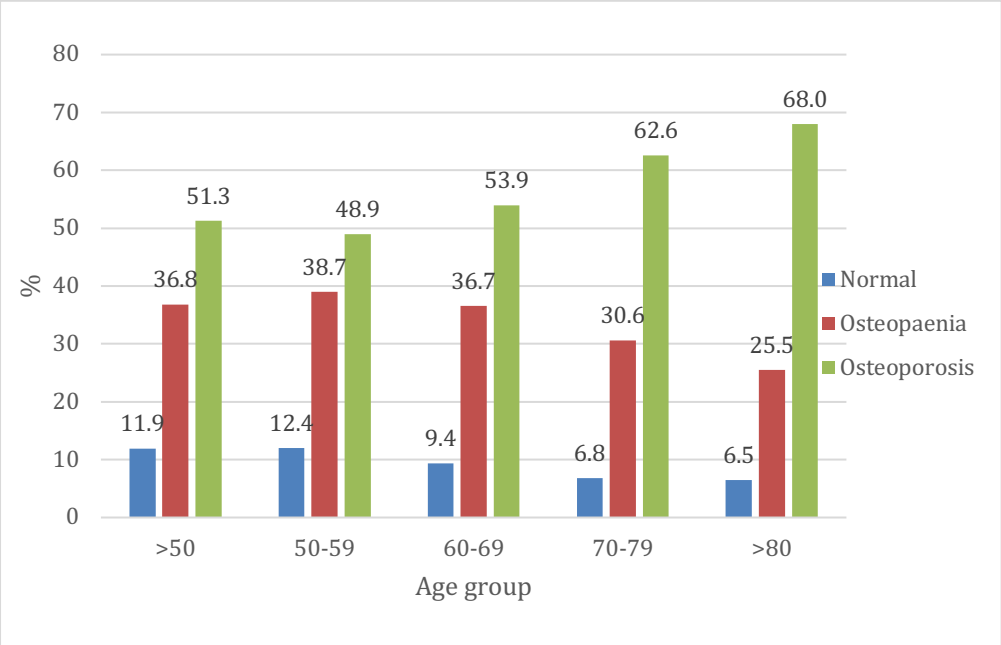


Figure 5: DXA diagnosis categorised by age group

2.3.4 Patient characteristics categorised by sex

Table 6: Differences in characteristics by sex

Patient characteristics (n)	**Male**	**Female**	**P-value**
Age, years (1724)	60.8±14	68.9±12.7	0.000
<50	34 (14.6%)	87 (5.8%)	
50-59	76 (32.8%)	251 (16.8%)	
60-69	57 (24.6%)	392 (26.3%)	
70-79	42 (18.1%)	443 (29.7%)	
80 and older	23 (9.9%)	319 (21.4%)	
Fracture history (1724)			
Vertebral fracture (1724)	55 (23.7%)	371 (24.9%)	0.703
Hip fracture (1724)	33 (14.2%)	230 (15.4%)	0.660
Body Mass Index (1343)	26.7±5.5	25.5±5.0	0.008
Underweight (18.5 kg/m^2)	9 (5.1%)	60 (5.3%)	
Normal (18.5-24.9 kg/m^2)	62 (35.2%)	504 (44.5%)	0.052
Overweight (25-30 kg/m^2)	62 (35.2%)	375 (33.1%)	
Obese (>30 kg/m^2)	43 (24.5%)	194 (17.1%)	
Medication history (1666)			
>5 medications	93 (42.5%)	507 (35.0%)	0.035
Osteoporosis treatment	56 (24.5%)	568 (39.5%)	0.000
Diagnosis by central DXA (1669)			
Normal	39 (17.2%)	109 (7.6%)	0.000
Osteopaenia	80 (35.2%)	474 (32.9%)	
Osteoporosis	108 (47.6%)	859 (59.5%)	
AP spine T score (1622)			
>-1	71 (32.4%)	222 (15,8%)	0.000
-1.0 to -<-2.5	67 (30.6%)	429 (30.6%)	
<-2.5	81 (37%)	752 (53.6%)	
Femoral neck T score (1081)			
>-1	43 (25.3%)	187 (20.5%)	0.377
-2.5—1	85 (50%)	487 (53.5%)	
<-2.5	42 (24.7%)	237 (26%)	
Total hip T score (1244)			
>-1	46 (28.4%)	235 (21.7%)	0.166
-2.5—1	69 (42.6%)	507 (46.9%)	
<-2.5	47 (29%)	340 (31.4%)	
Forearm T score (112)			
>-1	8 (44.4%)	9 (9.6%)	0.001
-2.5—1	2 (11.1%)	16 (17%)	
<-2.5	8 (44.4%)	69 (73.4%)	
QUS heel T score (1090)			
>-1	44 (29.5%)	147 (15.6%)	0.000
-2.5—1	63 (42.3%)	344 (36.6%)	
<-2.5	42 (28.2%)	450 (47.8%)	

Table 6 above demonstrates the differences in patient characteristics between males and females. Males were significantly younger (60.8 vs 68.9 years, P=0.000) and more likely to have higher mean BMI (26.7 vs 25.5, P=0.008) with a trend to being more obese (24.5 vs 17.1%, P = 0.052). Polypharmacy was more common in males (42.5 vs 35.0%, P=0.035) who were also more likely to be taking drugs for osteoporosis (39.5% v 24.5%, P=0.000). There was no difference in the prevalence of other fractures by sex but women were more likely to be diagnosed with osteoporosis (59.5% v 47.6%, P=0.000) and less likely to have normal BMD (7.6 vs 17.2% P=0.000). Similarly, when examined by site, females were more likely to have osteoporosis in the spine (59.5 vs 47.6%, P=0.000). Furthermore, the prevalence of an osteoporotic T score at the forearm was much greater in females (73.4 vs 44.4, P=0.001) who were also more likely to have T scores below -2.5 on US heel (P=0.000).

2.3.5 Predictors of BMD

Regression analysis was performed to clarify the contribution of age, sex and BMI to BMD at each site. For results see table 7 below.

Table 7: Regression analysis of predictors of BMD at all sites in patients after wrist fracture

	BMD Spine n=1284 R^2=0.16		**BMD FN** n=870 R^2=0.18		**BMD T Hip** n=962 R^2=0.31		**BMD forearm** n=95 R^2=0.46	
	β	p-value	β	p-value	β	p-value	β	p-value
Age	-0.001	0.000	0.003	0.000	-0.003	0.000	-0.006	0.000
Female	-0.096	0.000	-0.032	0.008	-0.028	0.019	-0.076	0.011
BMI	0.110	0.000	0.008	0.000	0.013	0.000	0.008	0.000

Age, sex and BMI were shown to be independent predictors of BMD at all sites though the effect size is small for age. Using this model 46% of the variation in BMD was explained at the forearm, 31% at the total hip, 18% at neck of femur and 16% at spine. When the analysis was performed in patients not on osteoporosis treatment the results were similar.

2.3.6 Other bone health parameters

Calcaneal QUS

1074 patients had DXA and QUS. Figure 6 below shows the QUS diagnostic categories by DXA diagnosis (normal, osteopenia and osteoporosis). The columns represent the diagnosis by standard DXA criteria. The colours within each column represent the proportion in each category identified by QUS. The concordance rate of QUS T score <-2.5 and osteoporosis on DXA was 57.5% and specificity was 73.5%. The positive predictive value of US using calculated T score of -2.5 was 75.9% and negative predictive value was 54.3%. We also noted that 14.6% of patients with a normal DXA have an QUS calculated T score below -2.5. Only 68 patients had both US heel and DXA forearm. T scores were in the osteoporotic range for both in 36 of these patients.

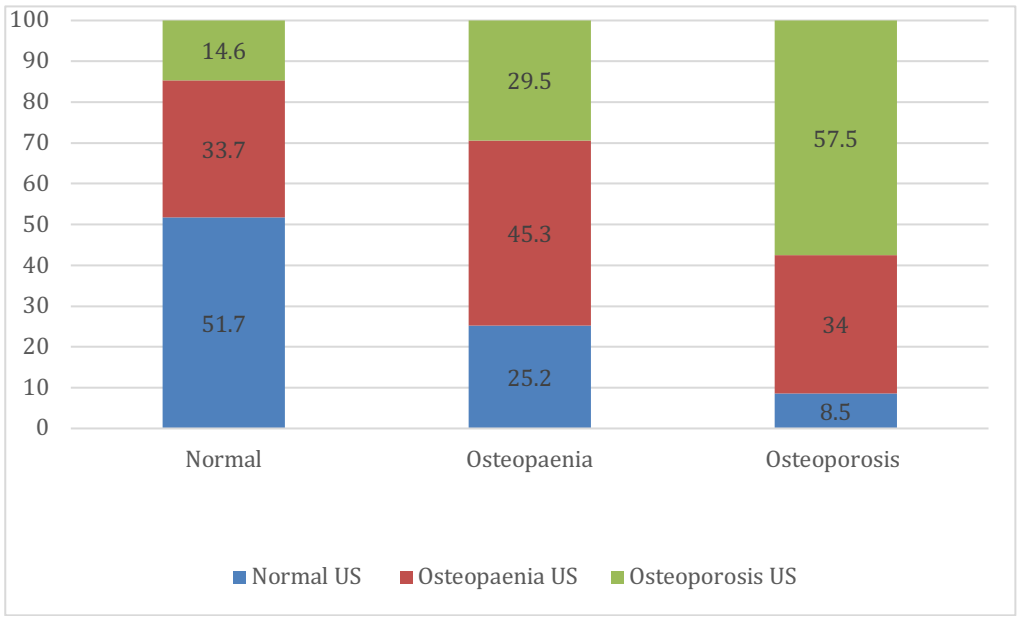


Figure 6: QUS results categorised by DXA diagnosis (n=1074)

Normal US: calculated T scores above -1; Osteopaenia US: calculated T scores -1 to -2.5; Osteoporosis US: below -2.5

Osteoporosis treatment

Table 8 shows patient characteristics dichotomised by treatment or no treatment. (ie use of an antiresorptive agent).

Table 8: Patient characteristics dichotomised by treatment or no treatment

Patient characteristics (n)	Treatment	No treatment	P value
Age , years(1666)	70.4 ±12.1	65.9 ± 13.6	0.000
BMI, kg/m^2 (1299)	25.0 +/- 4.9	26.1 +/- 5.0	0.000
Bone turnover markers (844)			
CTX (ngml)	0.235 ± .202	0.389 ± .23	0.000
PINP (ng/ml)	36.9 ± 31.6	58.3 ± 39.4	0.000
Osteocalcin (ng/ml)	19.39 ± 13.6	26.4 ± 13.6	0.000
ALPIU/L)	79.2 ± 40.1	86.5 ± 36	0.006
25(OH)D, nmol/l (1006)	75.1 ± 30.2	62.5 ± 30.4	0.000
< 30	31 (7.4%)	91 (15.5%)	
30-49.9	58 (13.8%)	116 (19.8%)	0.000
>50	330 (78.8%)	380 (64.7%)	
PTH, pg/ml (862)	46.1 ± 54	43.5 ± 27.5	0.354
>65	47 (12.2%)	54 (11.3%)	0.672
DXA diagnosis (872)			
Normal	18 (3%)	125 (12.4%)	0.000
Osteopaenia	148 (24.3%)	396 (39.3%)	
Osteoporosis	442 (72.7%)	544 (33.7%)	
T scores			
AP spine T score (1569)	-2.7 ±1.4	-2.1 ±1.4	0.000
FN T score (1052)	-2.01 +/- 1	-1.6 +/- 1	0.000
TH T scores (1205)	-2.2 +/- 1.1	-1.6 +/- 1.2	0.000
Forearm T score (108)	-3.3 +/- 1.5	-2.6 +/- 1.9	0.000
QUS heel T score (1052)	-2.5 +/- 1.2	-2.0 +/- 1.3	0.000

BMI: Body mass index, PTH: parathyroid hormone, FN: femoral neck, TH: total hip

Those on treatment were more likely to be older (70.4 vs 65.9 years, P=0.000) and have a lower BMI (25.0 v26.1 kg/m2, P=0.000). There was a significant difference in all bone turnover marker results. Those on osteoporosis treatment were more likely to have lower bone turnover markers; CTX 0.235 vs 0.389 ng/ml, PINP 36.9 vs 58.3 ng/ml, osteocalcin 19.39 v 26.40 ng/ml, ALP 79.2 vs 86.5 IU/L (P=0.000) Vitamin D levels were also more likely to be higher in those on treatment (75.1 v 62.5 nmol/l P=0.000) who were about half as likely to have vitamin D deficiency (7.4% vs 15.5%, P=0.000). At all DXA sites, patients on treatment also had lower T scores (Spine -2.7 vs -2.1, FN -2.0 vs -1.6, TH -2.2 vs -1.6, Forearm -3.3 v -2.6, US heel -2.5 vs -2.0) and were more likely to have osteoporosis (72.7 vs 33.7%, P=0.000).

2.4 Discussion

2.4.1 Patient characteristics

This study identfied that 86.3% of all distal forearm fracture occured in females in keeping with findi§ngs described elswhere (216). The mean age of patients was 67.8 years which also similar to other studes (158) Overall, we identified that 57.9% had osteoporosis and 33.3% osteopaenia by standard DXA criteria. The prevalence of osteoporosis in wrist fracture patients varies in the literature from 17% to 68% (see table 1). The prevalence shown in our study is similar to other Irish studies though at the higher end of what is reported internationally. Berginger et al showed that 45% of women with wrist fractures had osteoporosis in a study in Northern Ireland (159). A UK study published in 2008 reported that 32.9% of patients with wrist fracture had osteoporosis when defined as T scores less that -2.5 at either hip or spine. An Irish study of 100 females (aged over 60) with wrist fractures also showed that 68% of women had osteoporosis and 28% osteopaenia (158). The highest prevalence of osteoporosis in our wrist fracture patents was at the forearm at 68.7% (though sample size is small). It has been shown that site specific BMD better predicts fracture (217) (145).

Similar to our findings, patients with lower BMI were more likely to have lower T scores (158) (218). We also found that males with wrist fractures were less likely to have osteoporosis consistent with other studies where they had higher BMD, at both the hip and spine (219). Males were also younger by a mean of 8.1 years compared to females. A similar pattern has been shown in Scandinavian registry data (220). In our study, males were also more likely to be taking $\geq$5 medications suggesting a higher level of morbidity. Additionally, almost half of the males diagnosed with osteoporosis had anaemia. There was also a significant difference in rates of CKD though very few patients had CKD IV/V. It is possible that biomechanical factors may also explain some of this difference between sexes including the nature of trauma or level of impact leading to fracture. For example, males may be more at risk of greater trauma to the wrist. Other factors related to falls risk including alcohol consumption which may be greater in males might be important. It is also possible that older males, who are less likely to attend healthcare clinics (221), may not have been referred to our service.

Those with osteoporosis had higher ALP and CTX though there was no significant difference in osteocalcin or PINP. However, the small difference we found in BTM was marginal and might be chance finding. One third of wrist fracture patients had vitamin D levels below 50nmol/l. This prevalence of vitamin D inadequacy is significantly lower than reported in recent studies in Ireland (222) where it ranged from between 40-45%. However, our study included only adults aged >50 and many were likely to be taking supplements. Overall, we found that 11.5% in our cohort had hyperparathyroidism, likely due to low vitamin D status and possibly advancing renal impairment. However, there may have also been primary hyperparathyroidism in a very small proportion. Higher

rates of hyperparathyroidism have been shown in other studies of patients with wrist fracture (223) and also hip fracture (224). In fact, elevated serum PTH a risk factor for cortical bone loss at the forearm and also fracture (225). However, a retrospective study examining patients after wrist fracture, published in 2002, did not show higher rates of hyperparathyroidism compared with controls (226).

We showed that age, gender and BMI are significant predictors of BMD accounting for 16% of the variation at the hip but a much greater (46%) effect a the forearm The correlation between age and forearm BMD has been described elsewhere (227). In particular, female sex was the most significant predictor of forearm BMD which is expected given the negative effects of oestrogen loss due to menopause on bone. However, interesitingly BMI was also positively associated with forearm BMD. The relationship between BMI, BMD and fracture risk at diffferent sites is complex (228). In this study, lower T scores were associated with lower BMI which is generally reported elsewhere (229). However, we found that the majority of patients with forearm fracture were not underweight. Falls on the outstretched hand predispose to forearm trauma and therefore wrist fractures, though higher BMI may have the potential to increase this impact and fracture severity (153).

In this cohort, a quarter had a history of a vertebral fracture and one in six a hip fracture. This is a higher rate than is reported in some studies, with previous fracture rates of as low as 7.7% reported in some cohorts (230). However, this includes prevalent vertebral fractures identified by VFA when the patients attended the service. The role of VFA in this way to detect previously silent vertebral fractures was outlined in a recent position paper by IOF Fracture Working Group (119).

2.4.2 QUS Heel

We identified that calcaneal QUS (in 1074 patients who also had contemporaneous DXA) had sensitivity of 59% in diagnosing osteoporosis using a T score cut-off of -2.5. The positive predictive value of QUS for diagnosing osteopoross was 75.9%, using a T score of -2.5, and the negative predictive value was 54.3%. In this cohort, 14.6% of patients with normal BMD on DXA had a T score < -2.5 on QUS heel. Discordant results between heel QUS and DXA are not uncommon and are not necessarily an indication of methodological error. QUS measures other bone material properties rather than just bone mineral density and the result should be interpreted in the context of clinical risk (as advised by the ISCD). ISCD suggest that a normal heel QUS and few other clinical risk factors for fracture is reassuring and further evaluation may not be necessary.. Furthermore, QUS has been shown to predict wrist fracture at about the same accuracy as DXA (231).

2.4.3 Treatment

Only 37.5% of patients were taking an antiresorptive therapy on first attending the service. Patients who were on treatment were more likely to be older, female and have lower T scores. Many patients were likely to be started on treatment following the bone health clinic assessments. Nonetheless, the findings support the role of FLS in early evaluation of patients after wrist fracture, so that

treatment can be initiated in a timely fashion. Indeed, research has identified low levels of evaluation and treatment of patients following wrist fracture. For example it was found to be as low as 8.7% in a nationally representative study in Korea (232). In Ireland, it was estimated that out of 10 fracture liaison services recently surveyed in 2019, only 19% of the non-hip fragility fractures were captured (109). In particular, studies have shown the effectiveness of intervention at the time of presentation with a fragility fracture. Importantly, Fracture Liaison Services can educate patients and primary care providers on the importance of identifying osteoporosis and treatment to reduce the risk of further fractures (233).

2.4.4 Limitations

To our knowledge, this is the largest study examining bone health characteristics of patients who have sustained wrist fractures in Ireland and the UK and spans 15 years in one geographical location. It provides a comprehensive review not just in terms of clinical history but also investigations performed. Patient diagnostic work up included DXA with VFA and Calcaneal QUS, as well as a range of bone biochemistry including bone turnover markers, vitamin D, and serum PTH. However, there are a number of limitations in this study. Firstly, the patients included were referred from a number of sources including GPs and other doctors. This may have resulted in referral bias as patients with DXA defined osteoporosis after wrist fracture may have been more likely to attend. Secondly, there was missing data in a number of fields in our database which meant that sample sizes were smaller with regard to certain characteristics. In particular, restricted mobility may have resulted in fewer patients having BMD measured at the hip. Thirdly, data is not contemporaneous with wrist fracture occurrence. Fourthly, we did not have data on the circumstances that resulted in the wrist fracture, including the nature or mechanism of falls or other trauma.

2.4.5 Conclusion

The results highlight the high prevalence of osteoporosis (over 50%) in patients with wrist fracture with less than one in ten patients having normal BMD. We identified that of those with wrist fractures, females, older and underweight adults were more likely to have lower BMD. Furthermore, a quarter had a history of a vertebral fracture and one in six a hip fracture. Prior to attending the service approximately only a third of patients were on treatment for osteoporosis. In particular males, younger patients and those with better T scores were less likely to be on therapy. Findings highlight the "treatment gap" and importance of secondary prevention and need for systems to identify patients in whom future fracture risk should be assessed.

Chapter 3: Characteristics of patients attending a Bone Health Clinic with vertebral fracture(s)

3.1 Introduction

Vertebral fractures are the most common osteoporotic fracture though the majority do not present clinically and are therefore often missed. They have not been as extensively studied as some other fracture types. Furthermore, how vertebral fractures are defined radiologically and their true incidence and prevalence has been the subject of more recent studies Patients with recent vertebral fractures are up at up to 2-5 times increased risk for further vertebral fractures as well as double the risk of other fractures. Vertebral fractures are associated with significant morbidity and mortality. A recent meta-analysis based on placebo data of randomised clinical trials showed the biggest predictor of incident vertebral fracture was prevalent vertebral fractures (234).

The characteristics of patients who experience vertebral fractures are still being explored. It is important to be able to identify patients at high risk of fracture for primary and secondary prevention so as to target further investigations and treatment. Indeed, fracture liaison services often miss vertebral fractures given the high rate of fractures not presenting clinically. However, new technologies including artificial intelligence have been investigated in trying to opportunistically identify vertebral fractures in patients who have had radiological tests for other reasons. A recent systematic review was published considering the available literature regarding the epidemiology of vertebral fractures in Ireland and concluded that vertebral fractures are common and that prevalence is likely rising. It also concluded that further work is needed to explore the epidemiology of these fractures (122).

The aim of this study was to investigate the characteristics of patients with vertebral fractures who were attending our Bone Health and Osteoporosis Service. In particular, we aimed to establish the prevalence of osteoporosis by DXA criteria in the study population. We also aimed to describe the demographic features and bone health measures including QUS heel results, serum bone turnover markers and vitamin D levels. Finally, we also aimed to compare the characteristics of patients with vertebral fractures by sex and with patients who had wrist fractures attending our service (discussed in chapter 2).

3.2 Methods and materials (see chapter 2)

3.2.1 Study population

This included patients with vertebral fractures who were referred to the bone health service via a number of pathways; firstly, patients are referred from other hospital services and from general practitioners, secondly via our inpatient Fracture Liaison Service (FLS) and thirdly from our DXA service if a vertebral fracture is identified on VFA. Data regarding all patients seen in the service are recorded in the Bone Health and Osteoporosis Service Database. At the time of referral to FLS or to the bone health service, radiological investigations are reviewed and fracture(s) confirmed. All patients were included in this study if they had a vertebral fracture.

3.2.2 Data collection

The database was completed prospectively at the time the patient was assessed in the nurse led clinic by the Clinical Nurse Specialist. Data were collected regarding demographic details including age and sex, medical history and medications (at the time of visit). All patients were asked about previous fractures and where possible fracture history was confirmed by examining the radiology records in the hospital. Information was also recorded regarding specific medication used to treat osteoporosis. The results of blood investigations performed on the day including 25 hydroxyvitamin D (25(OH)D) and bone turnover markers (BTM) were recorded.

Biophysical measures

Weight was measured with a calibrated scale accurate to 0.1kg. Height was recorded using a stadiometer to the nearest 0.01m. Body Mass Index was calculated as per the standard definition (weight/height2). Measurements were obtained prior to DXA assessment.

QUS heel

We used the Achilles Insight (General Electric) to obtain calcaneal quantitative ultrasound (QUS) measurements. We use the calculated T score to describe the results. Quality control was conducted before each test as per manufacturer's specifications.

DXA

BMD was determined by a Lunar Prodigy DXA (Lunar Corp., Madison, WI) from 2004 until 2015 and thereafter by an Hologic Horizon A scanner. The DXA scans were obtained by standard procedures supplied by the manufacturer for scanning and analysis. All scans were performed by trained radiographers. Daily quality control was carried out by measurement of a lunar phantom. The reference standard from which the T-score is calculated is the female, white, aged 20-29 years in the NHANES III database. The output variables used for analysis were BMD (g/cm2) and T score. Forearm sites were assessed if there was a specific indication (hyperparathyroidism) or if other sites

of assessment were unavailable. Osteoporosis was defined as per standard definitions using central DXA sites (hip, femoral neck and spine) as discussed previously (see chapter 1).

Blood tests

Vitamin D and serum BTM

Vitamin D (25(OH)D) and parathyroid hormone (PTH), total alkaline phosphatase (ALP) and bone turnover markers (CTX, Osteocalcin, PINP) were measured. Morning blood samples for 25(OH)D and BTMs were taken on the day of assessment. Bloods were processed on the same day and centrifuged within two hours. Samples were stored at -20C and batched for later analysis at the biochemistry laboratory. The laboratory at SJH is a participant of the Vitamin D External Quality Assessment Scheme (DEQAS). 25(OH)D were measured by liquid chromatography mass spectroscopy (LCMS) using a standardised assay (Mass Chrom) and National Institute of Standards and Technology (NIST) vitamin D standard reference material. The inter and intra-assay coefficient of variation were 5.7% and 4.5%.

Other blood tests

Other blood tests were also performed including Full Blood Count. (FBC), renal, liver and bone profiles, serum protein electrophoresis, thyroid function tests, coeliac screen according to standard laboratory procedures. Haemoglobin results are categorised by the presence of anaemia; haemoglobin for females less than 11.5 g/dl and for males less than 13.5g/dl.

3.2.3 Statistical analysis

Data collected between December 2004 and January 2019 were analysed. Data was initially exported into Excel, cleaned, coded and then exported to SPSSv26 for analysis. Descriptive statistics included percentage for prevalence, means and standard deviations for normally distributed variables and medians and interquartile range for other variables. Patients were categorised by BMD status (normal, osteopaenia and osteoporosis) and the differences in characteristics between groups was analysed using ANOVA, t-test and chi square tests as appropriate. We also explored patient characteristics categorised by sex and analysed for differences with the above tests as appropriate. Predictors of spine BMD were explored in multiple linear regression models applying standard criteria including non-collinearity and normal distribution of predictor variables. Independent variables included age, sex and body mass index as they are known to be predictors of BMD in other studies.

Finally, we examined how patients with vertebral fracture(s) who attended our service compared to those referred specifically to our unit with wrist fractures. We categorised patients into three groups, (1) those with only vertebral fracture(s), (2) only a wrist fracture or (3) both a wrist and vertebral fracture and compared by demographic and biophysical characteristics as well as DXA diagnosis. Statistical analysis using ANOVA, chi square and t-tests were performed as appropriate.

3.3 Results

3.3.1 Patient inclusion

We identified 1779 patients with vertebral fractures who had attended our service between 2004 - 2019

3.3.2 Characteristics of patients with vertebral fracture

Table 9: Characteristics of patients with vertebral fractures attending BHC 2003-2019

Patient characteristics [n}	**Number (%)**
Sex [1779]	
Female	1359 (76.4%)
Male	420 (23.6%)
Age, years (1779)	Mean 71.7 ± 12.4
<60	266 (15%)
60-69	408 (22.9%)
70-79	576 (32.4%)
80 and older	529 (29.7%)
Fracture history (1779)	
Wrist	426 (23.9%)
Hip	350 (19.7%)
Body Mass Index (1364)	Mean 26.0 ±5.30
Underweight (<18.5 kg/m^2)	64 (4.7%)
Normal (18.5-25 kg/m^2)	591 (43.3%)
Overweight (25-30 kg/m^2)	421 (30.9%)
Obese (>30 kg/m^2)	288 (21.1%)
Medication history (1718)	
>5 regular medications	802 (46.7%)
Anti-osteoporosis medication	763 (44.4%)
DXA diagnosis (1727)	
Normal	154 (8.9%)
Osteopaenia	562 (32.5%)
Osteoporosis	101 (57.9%)
Spine T score (1644)	Mean -2.25 ±1.67
>-1.0	333 (20.3%)
-1 - -2.5	486 (29.6%)
<-2.5	825 (50.2%)
Femoral neck T score (1135)	Mean -1.9±1.1
>-1	220 (19.4%)
-1 - -2.5	553 (48.7%)
<-2.5	362 (31.9%)
Total hip T score (1330)	Mean -1.95 ±1.2
>-1	290 (21.8%)
-1 - -2.5	568 (42.7%)
<-2.5	472 (35.5%)
Forearm T score (148)	Mean-2.8±1.9
>-1	25 (16.9%)
-1 - -2.5	35 (23.6%)
<-2.5	88 (59.5%)
US heel T score (1130)	Mean -2.1±1.42
>-1	236 (20.9%)
-1 - -2.5	378(33.5%)
<-2.5	516 (45.7%)

Table 10: Characteristics of patients with vertebral fractures attending BHC 2003-2019 (Continued)

25(OH)D D (nmol/l) (1302) <30 30-49.9 >50	69.6±31 160 (12.3%) 205 (15.7%) 937 (72%)
Other Bloods	
PTH (pg/ml)	44.2±31.2
Serum Calcium (nmol/l) [1102]	2.33±.12
Phosphate (mmol/l) [1171]	1.03±.18
ALP (IU/L)	84.8±37.4
CTX (ng/ml)	0.297±.217
Osteocalcin (ng/ml)	21.6±13.3
PINP (ng/ml)	47.3±39
Hb (g/dL) (1168)	12.9±1.47
Cr (umol/l) (1191)	77.4 ±25

PTH: Parathyroid Hormone, ALP: alkaline phosphatase, CTX: C terminal telopeptide of type 1 collagen, P1NP: N terminal propeptide of type 1 procollagen, Hb: Haemoglobin, Cr: Creatinine

Demographics

The majority of the study population were female (76.4%) and the mean age was 71.7 ± 12.4 years. Those aged under 60 represented 15% of the sample, while approximately 20% were between 60-69, 20% between 70-79 and almost 30% over 80 years. The mean BMI was 26.0 kg/m2 and 52.0% were overweight with 20% being obese with BMI>30 and only 4.7% were underweight (BMI <18.5).

Medications

Of 1718 patients, 44.4% were taking or had taken prescribed antiosteoporosis medication. There was a median of four prescribed medications (n=1718) with the distribution of the number of medications taken by patients shown in Figure 5

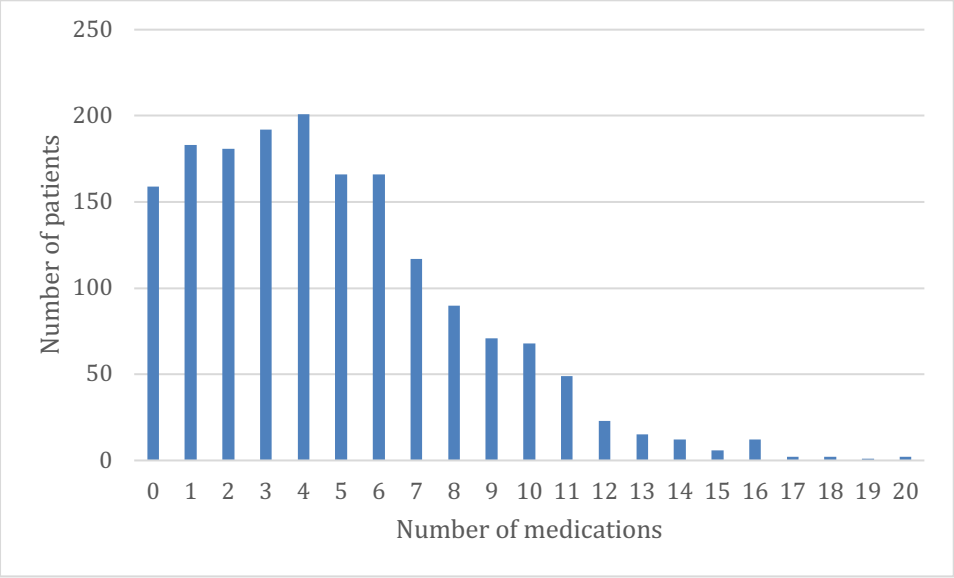


Figure 7: Distribution of number of medication taken by patients with vertebral fractures

DXA & QUS heel result & fracture prevalence

Table 9 summarises the DXA and QUS heel results for the population. DXA scans were performed on 97% of the sample (1727/1779). However, results were not available for all sites for a variety of reasons (e.g. inability to lie in scanner, bilateral hip prosthesis). The number of patients with a valid result for each site is outlined in the table. Less than in one in ten (8.9%) had normal BMD by central DXA, a third (32.5%) had osteopaenic and 57.9% had osteoporosis. Mean T scores were lowest in the spine (-2.25 ±1.67) followed by total hip-(1.95±1.20) and femoral neck (-1.9 ±1.0). Whereas, 50.2% had osteoporosis of the spine, this figure was 31.1% for neck of femur and 35.5% for total hip. Only 8.3% (148/1779) had a forearm DXA, and in two thirds of these patients T score was in the osteoporotic range. Using QUS heel T score results, a fifth (246/1130) were above -1, a third between -1 and -2.5 and 45.7% were less than -2.5. 19.7% had history of hip fracture and 23.9% a wrist fracture.

Blood test results

In those where vitamin D results were available (n-1302), 12.3% had deficiency (25(OH)D level <30nmol/l), 15.7% insufficiency (30-49.9nmol/l) and the remainder (72%) had replete status (>50 nmol/l). BTM results were available for the same patients mean CTX was in the therapeutic range <0.300. Mean serum calcium, and creatinine were also in the normal ranges.

3.3.3 Patient characteristics categorised by DXA diagnosis

Table 11: Patient characteristics categorised by DXA diagnosis

Patient characteristics (n)	**Normal**	**Osteopaenia**	**Osteoporosis**	**P-value°**
Sex				
Male (407)	59 (14.5%)	145 (35.6%)	203 (49.8%)	0.000
Female (1320)	95 (7.2%)	417 (31.6%)	808 (61.2%)	
Age group (1727)				
<60	33 (12.7%)	100 (38.6%)	126 (48.7%)	0.000
60-69	26 (6.5%)	150 (37.7%)	221 (55.7%)	
70-79	61 (10.9%)	182 (32.6%)	316 (56.5%)	
>80	34 (6.6%)	130 (25.4%)	348 (68%)	
Body Mass Index (1332)				
<18.5	0	3 (5%)	57 i7.1%)	0.000
18.5-24.9	17 (2.9%)	146 (34.8%)	408 (52.3%)	
25-30	45 (10.8%)	151 (47.3%)	220 (27.5%)	
>30	52 (18.2%)	119 (28.4%)	114 (14.2%)	
Wrist fracture (1727)				
Yes	20 (12.9%)	134 (23.8%)	261 (25.8%)	0.002
No	134 (87.1%)	428 (76.2%)	750 (74.2%)	
Hip fracture (1726)				
Yes	17 (11.0%)	88 (15.6%)	237 (23.4%)	0.000
No	137 (89.0%)	474 (84.4%)	773 (76.6%)	
Number of medication (1668)				
< 5	69 (46.0%)	290(53.2%)	526 (54.0%)	0.183
> 5	81 (54.0%)	255 (46.8%)	447 (46.0%)	
Antiosteoporosis medication (1618)				
Yes	33 (22.6%)	223 (41.8%)	484 (51.5%)	0.000
No	113 (77.4%)	310 (58.2%)	455 (48.5%)	
QUS heel T score (1111)				
>-1.0	55 (24%)	127 (55%)	48 (20.9%)	0.000
-1.0 -.2.5	35 (9.4%)	151 (40.5%)	187 (50.1%)	
<-2.5 correct	9 (1.8%)	102 (20.1%)	397 (78.1%)	

There were significant differences in the characteristics of patients with vertebral fracture when categorised by BMD status (ie osteoporosis, osteopaenia, and normal) (see table 11). Males were more likely have normal BMD (14.4 vs 7.2% p=0.000) and less likely to have osteoporosis (49.8 vs 61.2%, p=0.000). However, there was also a significant difference in BMI between groups. Mean BMI for patients with normal BMD was 29.8±4.7, osteopaenia 27.3±4.9 and osteoporosis 24.6±4.97 (p=0.000). A higher proportion of those with normal bone density had higher BMI. No patients with BMI <18.5 had normal BMD and 95% had osteoporosis. Approximately a fifth of those who were obese (BMI >30) had normal BMD, whereas 41.8% had osteopaenia and a further 40% osteoporosis. There were also significant differences between diagnostic categories depending on the age. For example, the mean age at time of presenting after vertebral fractures was 69.7±13.1 years in those with normal BMD but was higher in those with osteoporosis (73.2±11.8 years) (p=0.000). *T*here was an increasing prevalence of osteoporosis when patients also had a wrist fracture (62.9% vs 57.2% and vs p=0.002)) or hip fracture (69% vs 56%, p=0.000))

US heel

Both QUS heel and DXA results were available for 1111 patients. Concordance rate for normal BMD on both DXA and US heel was 4.9%. However, 76% of patients with a normal T score on QUS had osteopaenia or osteoporosis on DXA. The vast majority (96%) who had T scores between -1.0 and -2.5 on QUS had low bone mass on DXA, of which 40.5% had osteopaenia and 50% had osteoporosis. Finally, of the patients who had T scores <2-5 on QUS, 78.1% had osteoporosis on DXA. Using the standard T-score cut-off of -2.5, sensitivity of US heel for identifying osteoporosis in this cohort was 62.8% with a specificity of 76.8%, positive predictive value of 78.1% and negative predictive value of 61%.

Medication use and antiosteoporosis medication

There was no significant difference in the number of prescribed medications between groups. However, there was a greater proportion taking an anti-osteoporosis therapy who had DXA diagnosed osteoporosis (51.5%) versus osteopaenia (41.8%) or normal BMD (22.6%) (P=0.000).

3.3.4 Predictors of BMD

Regression analysis was performed to determine the contribution of different factors to BMD at each site and the results summarised below in table 12.

Table 12: Regression analysis of predictors of BMD at all sites in patients with vertebral fractures

	Spine		**Femoral Neck**		**Total Hip**		**Forearm**	
R^2	0.165		0.170		0.287		0.316	
	β	p	β	p	β	p	β	p
Age	0.000	.728	-0.003	0.000	-0.003	0.000	-0.004	0.000
Female	-0.110	0.000	-0.044	0.000	-0.055	0.000	-0.134	0.011
BMI	0.012	0.000	0.007	0.000	0.013	0.000	0.005	0.020

Using this model age, sex and BMI explained 16.5% of the variation in BMD at the spine, 28.7% at the hip and 31.6% at the forearm. Female gender had the greatest independent association at the forearm.

3.3.5 Characteristics of patients with vertebral fractures categorised by sex

There were significant differences in patient characteristics by sex (see table 13)

Table 13: Patient characteristics categorised by sex

Patient characteristics (n)	**Male**	**Female**	**P-value**
Age group (years)(1779)	n=420	n=1359	
<60	108 (25.7%)	158 (11.6%)	0.000
60-69	103 (24.5%)	305 (22.4%)	
70-79	125 (29.8%)	451 (33.2%)	
>80	84 (20.0%)	445 (32.7%)	
Body Mass Index (1345)	n=315	n=1049	
Underweight (<18.5 kg/m^2)	16 (5.1%)	48 (4.6%)	0.238
Normal (18.5-24.9 kg/m^2)	122 (38.7%)	469 (44.7%)	
Ovrweight (25-30 kg/m^2)	110 (34.9%)	311 (30.0%)	
Obese (>30 kg/m^2)	67 (21.3.%)	221 (21,0%)	
Wrist fracture (1779)			
Yes	55 (13.0%)	371 (27.2%)	0.000
No	365 (27%)	988 (73%)	
Hip fracture (1777)			
Yes	83 (23.7%)	267 (76.3%)	1.000
No	337 (23.6%)	1090 (76.4%)	
Number of medication (1718)			
<5	207 (22.6)	709 (77.4%)	0.233
>5	201 (25%)	601 (75%)	
Antiosteoporosis medication (1660)			
Yes	140 (35.4%)	623 (49.2%)	0.000
No	255 (64.6%)	642 (50.8%)	
Diagnosis by central DXA (1669)			
Normal	59 (38.3%)	95 (61.7%)	0.000
Osteopaenia	145 (25.8%)	417 (74.2%)	
Osteoporosis	203 (20.1%)	808 (79.9%)	

Table 14: Patient characteristics categorised by sex (continued)

Patient characteristics (n)	**Male**	**Female**	**P-value**
Spine T score (1622)			
>-1	116 (34.%)	217 (65.2%)	0.000
-1—2.5	115 (23.7%)	371 (76.3%)	
<-2.5	158 (19.2%)	667 (80.8%)	
Femoral neck T score (1081)			
>-1	69 (31.4%)	151 (68.6)	0.016
-1—2.5	140 (25.3%)	413 (74.7%)	
<-2.5	75 (20.7%)	287 (79.3)	
Total hip T score (1244)			
>-1	95 (32.8%)	195 (67.3%)	0.000
-1—2.5	127 (22.4%)	441 (77.6%)	
<-2.5	88 (18.6%)	384 (81.4%)	
Forearm T score (112)			
>-1	12 (10.7%)	13 (52%)	0.000
-1—2.5	9 (25.7%)	26 (74.3%)	
<-2.5	8 (9.1%)	80 (90.9%)	
QUS heel T score (1090)	N=266	N=864	
>-1	90 (33.8%)	146 (16.8%)	0.000
-1—2.5	99 (37.2%)	279 (32.3%)	
<-2.5	77 (28.9%)	439 (50.1%)	

The majority of the study sample were female (76.4%) as previously discussed though there were a number of differences between sexes. Males were significantly younger than females (67.4±13.7 vs 73±11.6 years, P=0.000) and constituted just 15.8% of those aged over 80. However, there was no difference in either mean BMI or BMI categories by sex. Males were less likely to be on antiosteoporosis medication at the time of assessment (35.4% v 49.2%, P= 0.000). While there was no significant difference in the proportion with hip fracture by sex, a much lower percentage of males had sustained a wrist fracture (27.3% vs 13.1% p=0.000). Female patients were more likely to have lower T scores at all sites and have a DXA diagnosis of osteoporosis (61.2% vs 40.6%, p=0.000). More women had QUS heel T scores below -2.5 also (50.1% vs 28.9%, P=0.000).

3.3.6 Patient characteristics by presence of wrist or vertebral or both fractures

Table 15: Characteristics of patients with wrist only, vertebral only or both fractures

Patient characteristics (n)	Wrist	Vertebral	Both wrist and vertebral	P-value
Gender (3079)				
Male	177 (13.7%)	365 (26.9%)	55 (12.9%)	0.000
Female	1119 (86.3%)	990 (73.1%)	373 (87.1%)	
Age (3079)	66.3 ± 13.3	71.5± 12.6	72.5± 11.5	0.000
BMI (kg/m2) (2379)	25.7± 5.1	26.1±5.5	25.6±4.7	0.131
Number of medications (1718)				
<5	828 (66.5%)	680 (52.2%)	238 (56.7%)	0.000
> 5	418 (33.5%)	622 (47.8%)	182 (43.3%)	
Antiosteoporosis medication (2881)				
Yes	429 (35.3%)	581 (45.7%)	184 (46.7%)	0.000
No	786 (64.7%)	689 (54.3%)	210 (53.3%)	
Bone diagnosis by DXA (2983)				
Normal	128 (10.2%)	134 (10.2%)	20 (4.8%)	0.009
Osteopaenia	418 (33.4%)	428 (32.6%)	136 (32.6%)	
Osteoporosis	706 (56.4%)	752 (57.2%)	261 (62.6%)	
Spine BMD (g/cm2)	0.897	0.912	0.875	0.005
Femoral neck BMD (g/cm2)	0.748	0.716	0.714	0.000
Total hip BMD (g/cm2)	0.810	0.785	0.763	0.000
Spine T score (2870)				
>-1	234 (19.1%)	276 (22.1%)	59 (14.8%)	0.004
-1—2.5	384 (31.4%)	374 (30%)	112 (28%)	
<-2.5	604 (49.4%)	112 (47.9%)	229 (57.3%)	
Femoral neck T score (1958)				
>-1	192 (23.4%)	182 (20.8%)	38 (14.6%)	0.000
-1—2.5	441 (53.8%)	424 (48.3%)	131 (50.2%)	
<-2.5	187 (22.8%)	271 (30.9%)	92 (35.2%)	
Total hip T score (2265)				
>-1	223 (24%)	233 (22.8%)	58 (18.5%)	0.003
-1—2.5	444 (47.7%)	439 (43%)	132 (42.2%)	
<-2.5	264 (28.4%)	349 (34.2%)	123 (39.3%)	
Forearm T score (220)				
>-1	13 (18.3%)	21 (19.4%)	4 (9.8%)	0.182
-1—2.5	11 (15.5%)	28 (25.9%)	7 (17.1%)	
<-2.5	47 (66.2%)	59 (54.6%)	30 (73.2%)	

Table 16: Characteristics of patients with wrist only, vertebral only or both fractures (continued)

Patient characteristics (n)	Wrist	Vertebral	Both wrist and vertebral	P-value
QUS heel T score (1936)				
>-1	150 (18.7%)	195 (23%)	41 (19.9%)	0.000
-1—2.5	325 (40.5%)	299 (35.3%)	82 (28.5%)	
<-2.5	327 (40.8%)	352 (41.6%)	165 (57.3%)	
Hip fracture (3076)				
Yes	174(13.4%)	262(19.4%)	89(20.8%)	0.000
No	1121(86.6%)	1081(80.6%)	339 (79.2%)	
Blood results				
CTX (ng/ml)	0.310 ±.20	0.285±.20	0.299±.23	>0.05
Osteocalcin (ng/ml)	23.1±13.1	20.8±12.3	21.8±13.9	0.000
PINP (ng/ml)	47.5±31.5	45.3±35.5	21.8±13.9	>0.05
ALP (IU/L)	81.1±35.9	82.4±35.9	83.6±36.2	>0.05
Vitamin D (nmol/l)	65.8±30.7	70.5±30.4	68.1±31.9	0.000

DXA: Dual-energy X-ray Absorptiometry, BMD: Bone Mineral Density, BMI: Body Mass Index, PTH: Parathyroid Hormone, ALP: alkaline phosphatase, CTX: C terminal telopeptide of type 1 collagen, P1NP: N terminal propeptide of type 1 procollagen, Hb: Haemoglobin, Cr: Creatinine

Demographics

There was a significant difference in sex between fracture groups with significantly more men having only vertebral fractures (27% v 13-14%, P=0.000). Females were seven times more likely to have a history of a both a wrist and vertebral fracture (87 vs 13%). Similarly, a history of a wrist fracture was six times more prevalent in females compared to males (86 vs 14%).

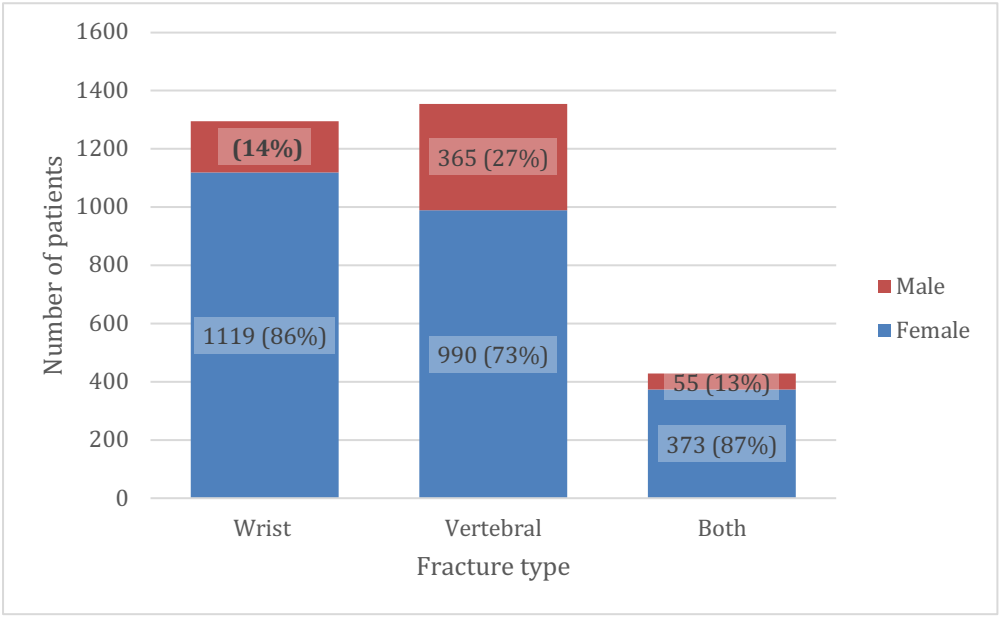


Figure 8: Proportion of patients with wrist, vertebral or combined (vertebral and wrist) fractures by gender

Those with wrist fracture were youngest (66.3±14.3 years) with increasing age for vertebral (71.5 ± 12.6 years) and both vertebral and wrist fractures (72.5± 12.1 years). Wrist fractures were the most common fracture up until the age 60-69, with the proportion then remaining static between the ages 70-79 followed by a substantial reduction at age 80 and older. There was a significant and continued rise in vertebral fractures from the age of 50+ (see figure 9).

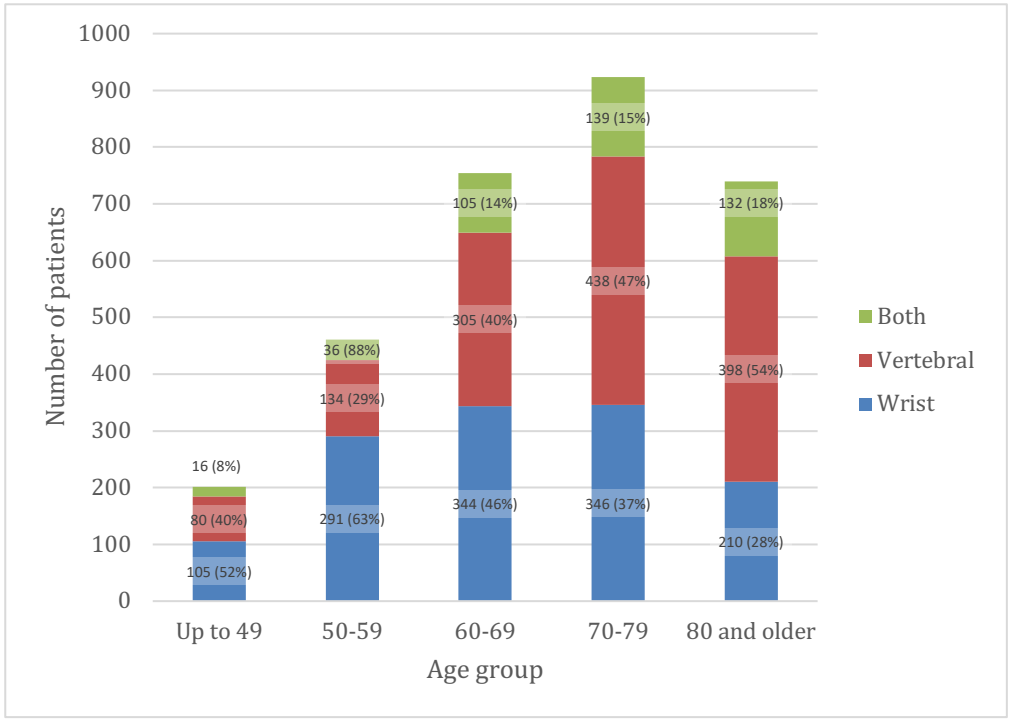


Figure 9: Proportion of wrist, vertebral and combined (vertebral and wrist) fractures by age

There was no difference observed in BMI by patient fracture history. However, in a separate analysis, those with fracture of the wrist and vertebrae versus wrist only were more likely to be of shorter stature (157±9.4 vs 159±8.7cm, P=0.000).

Polypharmacy and anti-osteoporosis medication

Polypharmacy was significantly lower in those with only wrist fractures (33.5%) compared to vertebral or wrist and vertebral (P=0.000). While 35% of patients with a wrist fracture were on anti-osteoporosis therapy, this increased to 45% with vertebral fractures and 46.7% in those with both wrist and vertebral fracture history (P=0.000). More than half of patients with multiple fractures were not taking antiosteoporosis medication.

Hip fractures

Hip fractures were more prevalent in those with a vertebral fracture (20.8%) or vertebral and wrist fracture (19.7%) versus wrist fracture only (13.7%)

BMD

The proportion of patients with central DXA diagnoses of normal BMD, osteopaenia and osteoporosis is shown in figure 10. Most patients who had a wrist and vertebral fracture had osteoporosis (63%) with only 5% having normal BMD. A lower proportion of patients had osteoporosis in the two other groups (56% - 57%). Approximately one third of patients in each group had osteopaenia on DXA.

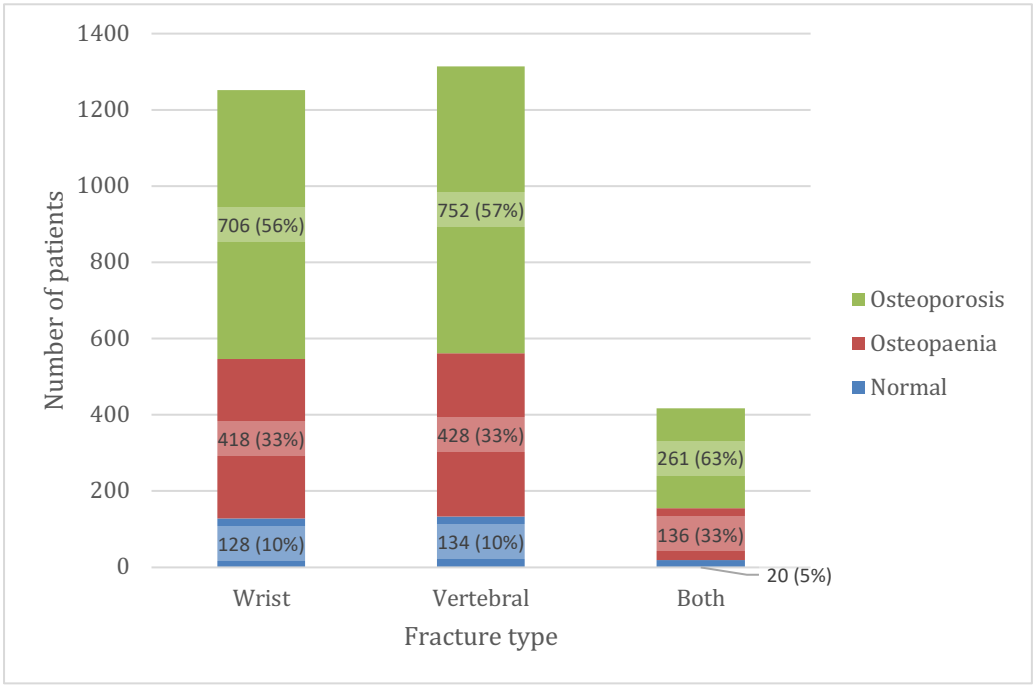


Figure 10: Proportion of wrist, vertebral and combined fracture by DXA diagnosis

When looking at site specific BMD, those with both fractures had lower BMD at the spine versus the other groups (P=0.000). In patients with wrist fractures only, total hip and femoral neck BMD was greater compared to the other groups (P=0.000).

Blood test results

There was no difference in BTM by fracture history except for osteocalcin which was marginally higher in wrist fracture patients (23.1ng/ml vs 20.8ng/ml in vertebral and 21.8ng/ml in both, P=0.000). Mean vitamin D levels were lowest in those with wrist fracture at 65.8 nmol/l vs 70.5 nmol/l in vertebral and 68.1nmol/l in both (P=0.000).

3.4 Discussion

3.4.1 Patient characteristics

The prevalence of osteoporosis by central DXA in patients with vertebral fractures was 57.9% with about a third (32.5%) having osteopaenia. Multiple studies have shown the association between BMD and vertebral fractures including increased severity and number of fractures with lower hip T scores (235). The prevalence of osteoporosis in patients with vertebral fractures varies in the literature likely reflecting the heterogenous design of vertebral fracture studies and the wide range of diseases and other factors contributing to the occurrence of vertebral fractures. In the Fracture Intervention Trial, 61% of patients with vertebral fracture had densitometric osteoporosis at the femoral neck which compares to 31.9% in our cohort. The mean BMD (g/cm^2) at the spine was 0.75 $\pm$ 0.13, and at the femoral neck was 0.54$\pm$ 0.07, much lower than in our cohort. However, a recently published Irish study reported a lower prevalence of osteoporosis on central DXA of 43.1% (236). This group has some similar characteristics including gender, age and BMI, though a significantly higher rate of prior fracture and a higher proportion were on antiosteoporosis medication at the time of assessment possibly suggesting that the BMD at the time was greater due to treatment. Their group had a high prevalence of rheumatoid arthritis which is risk factor for vertebral fractures independent of BMD. It is also likely that our population had lower BMD as it includes patients referred to a tertiary clinic for assessment for anabolic therapy. Similar BMD values have been identified in other non-Irish studies (237). Vertebral fractures commonly occur in patients with osteopaenic range BMD results. Degenerative disease including osteoarthritis can contribute to higher BMD readings (238). On QUS heel, 45.7% of patients had calculated T score less that -2.5 and a further 33.5% were in the osteopaenic range. US heel results have been shown to be predictors of vertebral fracture risk (239).

We found that between 16 and 31% of the variation of BMD on DXA at each site in our study was explained by three factors; age, gender and BMI. We found a clear association between age and increasing vertebral fracture prevalence as is consistently reported internationally. A study of postmenopausal Chinese females showed a radiographic vertebral fracture prevalence of 13% in those aged 50-59 rising to over 50% after the age of 60 (240). Similar findings have been also been shown in Caucasian populations (241).

The gender differences in incidence of the fracture is also consistent with the existing literature as 76% in our study were women (242). There were also differences between the men and women who had vertebral fractures. Men were younger, had higher BMD, were less likely to be on antiosteoporosis medication and have had a wrist fracture but had similar BMI. It has previously been shown that the probability of a man having a vertebral fracture was observed at higher absolute areal BMD than those observed for women (243).

We found no difference in mean BMI between those with vertebral fractures versus only wrist fracture. However, the relationship between BMI and fracture risk is complex. In some studies abdominal weight might increase vertebral fracture risk via increased loading in the spine, bone marrow fatty infiltration, increasing cytokine production and microarchitectural deterioration. A recent metanalysis also explored the relationship between BMI and vertebral fractures (244). Six studies were included with a total of 105,129 participants. An inverse association between BMI and risk of vertebral fracture in men was found but not in women. Ankle fracture incidence has been shown to be associated with higher BMI (245). However, some studies show that increased BMI might be protective for wrist fractures, while others show no effect on wrist fracture incidence. However, there is some evidence that increased BMI may be associated with more complex wrist fractures (246). Importantly, we did not do an analysis comparing BMI in vertebral fracture versus non-fracture patients and were also not able to adjust for several fracture risk factors.

3.4.2 Prevalence and characteristics of patients with different fracture types

One quarter of the patients in our study with vertebral fractures also had a wrist or hip fracture A recent study identified a similar proportion of patients presenting with non-vertebral low trauma fractures who had vertebral fractures (247). We again demonstrated a clear association with gender and age with both fractures significantly more frequent in females and especially wrist fractures Wrist fracture prevalence increased from the age of 50 with frequency plateauing at 60 as opposed to a sustained increase in vertebral fracture prevalence from the age of 60. The reduction in wrist fractures as patients reach older age is thought to be due to changes in the biomechanics of falling, neuromuscular control, walking speeds, onset of dementia, with older adults less likely to fall on an outstretched hand (248). We observed higher rates of polypharmacy in patients with vertebral fracture versus wrist fractures alone, suggesting the role of multimorbidity in increasing fracture risk. Patients were more likely to have had a hip fracture if they had a previous vertebral fracture than if they had a wrist fracture alone. We also observed significantly lower BMD and higher prevalence of osteoporosis in patients with vertebral or wrist and vertebral fractures compared to patients with wrist fractures alone. This may be in part explained by the younger age of the wrist only cohort and the possibility of the wrist fracture presenting as a “signal” fracture in these patients. Patients were more likely to be taking antiosteoporosis medication if they had vertebral fracture which probably relates in part to more having a DXA diagnosis of osteoporosis, Additionally, a high proportion were probably clinical vertebral fractures attending our clinic as opposed to being incidentally diagnosed on imaging. Possibly related to treatment, patients with vertebral fractures had slightly higher serum 25(OH)D levels. However, over half the patients with both fractures were not on antiosteoporosis medication. This treatment gap in the management of osteoporosis is well described as discussed in chapter 1.

3.4.3 Limitations

There are a number of limitations to this study. Firstly, patients were referred via the FLS, GPs and other physicians and therefore may not be representative of the wider population, to which the results may not be generalisable. Secondly, this is a cross-sectional study with data collected at a single time point, the patients first attendance at the bone health and osteoporosis unit. We do not have information on the timing of fractures and the data is not contemporaneous. However, patients are typically seen within 3-9 months of fracture at our clinic. We also have no follow up data available therefore precluding us from examining incident fracture risk, response to treatment and other outcomes. Thirdly, we did not have comprehensive data on site, severity or number of vertebral fractures or if the fractures were associated with trauma or presented clinically. We also have limited data on medical history and medications including steroids, or therapies known to cause bone loss such as androgen deprivation therapy or aromatase inhibitors. Additionally, data on other risk factors for vertebral and other fractures including rheumatoid arthritis and diabetes mellitus were not available. We also did not have information on frailty markers or functional status of the patients. Finally, while this is a relatively large study, there was missing data in a small proportion of patients which could also bias results.

3.4.4 Conclusion

A high proportion of patients with vertebral fracture, wrist fracture or both fractures have osteoporosis by DXA criteria and about a quarter had a history of other fractures. Only a small proportion of patients were taking treatment for osteoporosis, even in patients with multiple fractures. Patients were more likely to be taking antiosteoporosis medication if they had a vertebral fracture versus wrist fracture despite similar rates of DXA diagnosed osteoporosis. This may reflect the view that a wrist fracture is a perceved as a benign injury and less likely to be associated with osteoporosis or increased incident fracture risk.

3.4.5 Clinical implications/Future studies

This study adds to the research regarding the characteristics of patients with vertebral fractures. More studies are required to explore the predictors of vertebral fractures and target evaluation and preventative strategies accordingly. It is important that clinicians assessing older adults are aware that the presence of vertebral fracture(s) is a marker of significant osteoporosis. Furthermore, a significant proportion of patients with vertebral fracture(s) have already sustained other fractures, are at high risk of incident fragility fractures and need evaluation for potent treatments for osteoporosis, including teriparatide. Importantly, recognition of vertebral fractures provides an opportunity to intervene to reduce the risk of further fractures and their sequelae.

Chapter 4: Characteristics of patients attending SJH following distal forearm fracture

4.1 Introduction

Distal forearm fractures or wrist fractures include fracture of the radius and/or ulna. They are often the result of a fall on the outstretched hand and in older adults are often considered to be fragility fractures. Patients who sustain a fragility fracture of the wrist are at risk of having low bone mineral density and are at higher risk for future fracture. Thus, it is recommended that all patients over 50 years who sustain a low trauma wrist fracture should be evaluated and depending on future risk started on anti-fracture therapy.

Currently in Ireland, FLS is significantly underdeveloped and a national strategy is being developed to optimise the care of older adults following fragility fractures (109). Systematic identification of patients with fragility fractures and appropriate investigations and interventions reduces future fracture risk and is cost effective. A nation specific "scorecard" with regard to bone health management was compiled for countries in Europe recently and shows that progress has been made in Ireland in the last decade and highlights the importance of developing a national FLS strategy that invests in primary and secondary prevention of fractures (6).

A study of the characteristics of patients with wrist fractures in Ireland was conducted in 2007 (158). Since then, a number of studies have been published primarily regarding anaesthetic and surgical techniques (249). However, we do not have up to date data on the demographic or clinical characteristics of older adults presenting with distal forearm fracture.

In this study, we aimed to investigate the demographic and clinical characteristics of patients aged over 50 presenting to SJH with a wrist fracture.

4.2 Methods and materials

4.2.1 Patient selection

Patients sustaining wrist fractures and who presented to SJH were identified using the National Integrated Medical Imaging System (NIMIS). All distal forearm imaging performed each week was reviewed during the study period between January 2018 and October 2018. All patients who had an x-ray of the wrist and had a report that mentioned fracture were identified. Patients aged over 50 with a fracture of the distal radius or ulna were included if the fracture occurred in the context of low trauma. Low trauma was defined as a force equivalent to a fall from standing height or less. Patients were excluded if life expectancy was very short which included those diagnosed with a terminal illness and/or receiving palliative or end of life care. Patients were also excluded if they did not live in the province or country as they may not have been able to attend the assessment(s). They were also excluded if it was not possible to establish contact, or if the patient declined consent or did not attend any of the appointments.

4.2.2 Patient recruitment

Patients were invited by letter to participate in the study. A follow up phone call was then made within two weeks to arrange appointments. All appointments were planned to be conducted within at least 8-12 weeks of the fracture or as soon as the patient was available. The participants attended the Fracture Liaison Service (FLS) for assessment and were assessed at the time of their appointments. FLS clinics are held weekday mornings in the Bone Health Unit in St James Hospital. I was very flexible with appointment arrangements to facilitate patients requiring assistance and patients were included if they were able to attend at any stage in the first six months following the fracture. If the patient did not attend a DXA or assessment appointment they were contacted by phone where possible and offered another appointment if they were still interested in participating.

4.2.3 Data collection

Patient interview

Initial data collection included a 90 minute assessment. Data was recorded regarding age, sex and comorbidities. Charlson Comorbidity Index (CCI) (250) was calculated for each patient with the online version of the calculator used (251) (see appendix A). The names and number of regular medications was recorded for each patient. We also recorded social and bone health history including information on risk factors for osteoporosis and fracture. Regarding steroid use, dose and duration of therapy was also recorded. “Long-term steroid use” was defined as past or present exposure of three months or more, or daily dose use of 5 mg or more of prednisolone or equivalent. We recorded if the patient met the referral criteria for DXA (as per ISCD) prior to sustaining the fracture (13) (appendix B). Details of the injury including circumstances and associated injuries and treatment including surgery and/or rehabilitation completed was also recorded. Mini Mental State Examination (MMSE) (252) was completed where possible except in some patients who expressed

a desire not to complete it (see appendix C). The Clinical Frailty Scale (see appendix G) was applied to each patient (253). The Clinical Frailty Scale (CFS) is a judgement-based frailty tool that evaluates specific domains including comorbidity, function, and cognition to generate a frailty score ranging from 1 (very fit) to 9 (terminally ill). Dietary calcium intake was estimated using the online CGEM calcium calculator and expressed as mg per day (254) (see appendix D).

Biophysical Measurements

Weight and height

Weight was measured with a calibrated scale accurate to 0.1kg. Height was recorded using a stadiometer to the nearest 0.01m. Body mass index (BMI) was calculated as per the standard definition (weight/height^2). Measurements were obtained prior to assessment with DXA.

Timed Up and Go

Timed Up and Go (TUG) (255) was recorded where possible. This is a test where the time is measured from when the participant gets up from sitting, walks three meters, turns around and returns to the seated position in the same chair.

Grip strength

Grip strength was measured for all patients using the same Jamar dynamometer. The participant was asked if they would complete the test using both hands. A number of patients preferred not to attempt the grip strength tests due to pain or fear they would injure themselves given their recent wrist fracture. In these cases, the non-fractured hand only was assessed. The same technique was used for all assessments as done elsewhere (256). The Jamar Hand Dynamometer has a dual scale readout which displays isometric grip force from 0-90kg (0-200lb). It has a peak hold needle which automatically retains the highest reading until the device is reset. The second handle position was used for all participants and hand dominance and side of fracture was recorded. The patient was assessed in a seated position with their feet placed flat on the floor and shoulder adducted, elbow flexed at ninety degrees with the forearm and wrist neutral. The device was placed in the palm of the hand with the handle resting on the middle of the four fingers. We checked that the instrument felt comfortable and that the needle was reset prior to asking the patient to squeeze the device as tightly as they could and for as long as possible ensuring each squeeze was at least five seconds. We ensured grip force was applied smoothly. The result was recorded in kilograms (kg) with three measurements taken on each hand and the mean of each then calculated. Low grip strength was defined as <16kg for women and <27kg for men.

Lying and standing blood pressure

Lying and standing blood pressure was assessed. The same sphygmomanometer was used for each patient and measurements were taken while lying down and again at one, three and five minutes after standing. Orthostatic hypotension was defined as a systolic blood pressure decrease of at least 20mmHg or a diastolic blood pressure drop of at least 10mmHg within three minutes of standing (257).

DXA

DXA scans were performed on all patients who have not had a DXA in the previous six months on the Hologic Horizon DXA scanner in our department. The DXA scans were obtained by standard procedures supplied by the manufacturer. Daily quality control was carried out by measurement of a lunar phantom. All scans were performed by trained radiographers. The reference standard from which the T-score is calculated is the female, white, aged 20-29 years in the NHANES III database. AP spine, femoral neck, total hip and three forearm sites were evaluated in all patients. In keeping with ISCD recommendations 1/3 forearm was the primary forearm site used. The outcome variables recorded were areal BMD (g/cm^2) and T score.

QUS Heel

QUS heel of right heel was performed using the same machine for each patient as outlined in chapter 2.

Blood tests

Each patient had blood samples taken including full blood count (FBC), renal, liver and bone profile, Erythrocyte Sedimentation Rate, (ESR) serum protein electrophoresis, and Tissue Transglutaminase IgA (TTG). Bone turnover markers (CTX, PINP, Osteocalcin), parathyroid hormone level (PTH) and serum vitamin D (25OHD) were measured on samples separated and frozen at the time of the blood draw and batched for later analysis as described in chapter 2. All blood tests were taken in the morning.

4.2.4 Statistical analysis

Statistical analysis was performed using SPSSv26. Patient demographics were examined as well as clinical characteristics, fracture type and risk factors for osteoporosis. Means and standard deviations were used where data were normally distributed, or otherwise medians and interquartile ranges. We compared patient characteristics by sex, DXA diagnosis and osteoporosis treatment (yes/no) using chi square, ANOVA, unpaired t-test and Mann-Whitney U tests as appropriate. We also looked at associations with previous fracture history, falls and early menopause in univariate regression analysis.

4.3.5 Ethical approval

Ethical approval was granted on the 11 January 2018 by the Joint SJH/Tallaght Research and Ethics Committee in Tallaght Hospital.

4.3 Results

4.3.1 Participant inclusion

Overall, 244 patients were identified with wrist fractures, of which 111 were excluded leaving 133 in this study. Reasons for exclusion are summarised in the table 17 below.

Table 17: Reasons for patient exclusion from study

Exclusion criterion	**Number of patients (n=111)**
Did not attend or cancelled >3 appointments	22 (19.8%)
Unable to contact patient	18 (16.2%)
Declined consent	18 (16.2%)
Fracture associated with significant trauma	17 (15.3%)
Not resident in the region or country	16 (14.4%)
Very limited life expectancy	10 (9%)
Died before initial assessment completed	6 (5.4%)
Old fracture (more than one year ago)	3 (2.7%)

4.3.2 Summary of participant characteristics

Table 18: Baseline characteristics of the prospective wrist fracture cohort (n=133)

Characteristic	No of patients (%)
Sex	
Female	124 (93.0%)
Age, years (mean)	69.3 ± 11.0
<70	74 (55.6%)
Dominant hand fracture	62 (46.6%)
Living alone	36 (27.1%)
Comorbidities	
Hypertension	44 (33%)
Hyperlipidaemia	32 (24%)
COPD	20 (15%)
Osteoarthritis	15 (11%)
Dementia	6 (4.5%)
Charlson Comorbidity Index	
1	20 (15.0%)
2	27 (20.3%)
3	33 (24.8%)
4	30 (22.6%)
5	13 (9.8%)
6	7 (5.3%)
7	2 (1.5%)
10	1 (0.8%)
Clinical Frailty Scale	
1 Very fit	65 (48.9%)
2 Well	20 (15.0%)
3 Managing well	12 (9.0%)
4 Vulnerable	16 (12.0%)
5 Mildly frail	5 (3.8%)
6 Moderately frail	6 (4.5%)
7 Severely Frail	9 (6.8%)
MMSE (mean) (n= 68)	26.7 ± 4.5
Falls history	
Recurrent falls	31 (23.3%)
Symptoms of orthostatic hypotension	38 (28.6%)
Number of medications	
None	12 (9.0%)
1-4	68 (51.1%)
≥5	53 (39.8%)

Table 19: Baseline characteristics of the prospective wrist fracture cohort (n=133) (continued)

Characteristic	No of patients (%)
Risk factors for osteoporosis	
Previous fracture	62 (45.9%)
Vertebral fracture	17(12.8%)
More than one previous fracture	13 (9.8%)
Early menopause (<45 years)	53 (39.8%)
Low dietary calcium (<700mg per day)	53 (39.8%)
Height loss	44 (33.1%)
Family history	40 (30.1%)
Low body weight (BMI<18.5 kg/m2)	32 (24%)
Current smoker	24 (17.8%)
Alcohol (>14 units a week)	18 (13.5%)
Long term steroid (>3 months)	4 (3.0%)
Antiosteoporosis medication prior to injury	29 (12.8%)
Bisphosphonate	24
Denosumab	9
Recombinant PTH	2
>1 prior treatment	6
On treatment at the time of injury	18

Table 20: Regular medications per patient in prospective wrist fracture cohort (n=133)

Number of medication	Frequency (%)
0	12 (9.0%)
1	16 (12%)
2	23 (17.3%)
3	15 (11.3%)
4	14 (10.5%)
5	9 (6.8%)
6	7 (5.3%)
7	4 (3.0%)
8	7 (5.3%)
9	8 (6.0%)
10	2 (1.5%)
11	7 (5.3%)
12	4 (3.0%)
13	6 (3.8%)

4.3.3 Demographic characteristics

Of the 133 patients who attended for assessment, 93.0% were female and all were Caucasian. The age of participants ranged from 50-92 years with a mean of 69.3 years. A quarter (27%) of patients were living alone at the time of the fracture. Over half the patients (68/133) or, 51.1% completed the MMSE with 42.9% achieving a score (>24).

4.3.4 Fracture characteristics

Approximately half (45.1%, 60/133) of the participants had fractured their right wrist, with a further 53.4% (71/133) fracturing their left wrist and two sustaining fractures bilaterally. About half (62/133) fractured their dominant wrist and 14.3% (19/133) had sustained another injury at the same time of their wrist fracture. This included 5 patients with hip fractures, 3 pelvic fractures and 3 vertebral fractures.

4.3.5 Indicators of general health

The most frequently reported comorbidity in the cohort was hypertension, identified in 32.6% of the participants. Hyperlipidaemia and COPD were also quite commonly reported, 23.7% and 14.8% respectively. Six patients with diagnoses of dementia prior to the fracture were also included in the study.

Comorbidities were also evaluated using the Charlson Comorbidity Index (CCI) as previously described. The majority of participants had a CCI of <3. The most frequent scores were three (24.6%), four (23%), and two (20.1%). 17.0% of patients scored over 5 indicating a higher mortality risk. We also applied the Clinical Frailty Scale to the cohort as shown in table 18 above. The majority (72.9%) of patients were not frail (CFS≤3), 12% were vulnerable (CFS 4) and 20 (15.1%) were frail with nine patients (6.8%) being were severely frail.

Another indicator of the health was the number of regular medications they were taking. A high proportion (39.9%) of the participants had polypharmacy (≥5 medications). The majority of patients (83.5%) reported that they were independent with personal activities of daily living prior to their fracture.

4.3.6 Bone health history

Fracture history and risk factors

Almost half (62/133, 45.9%) of the patients included had previously sustained a clinical fracture and of these 13 also reported a history of more than one prior fracture. Seventeen patients (12.8%) had evidence of vertebral fracture on VFA assessment using DXA.

Those who had had a previous fracture were more likely to have polypharmacy (45% vs 22.5%, P=0.010) but there was no difference in sex (P=0.502), age (P=0.690) or frailty (P=0.344). However, they were more likely to have a DXA (55.7% vs 30.2%, P=0.003) and to be on treatment for osteoporosis (32.9% vs 9.5%, P=0.001). There was no difference though in current DXA diagnosis (P=0.254) or BTM (P=0.659) when dichotomised by previous fracture history. In addition, no risk factor for osteoporosis was found to be significantly associated with previous fracture including family history (P=0.667), early menopause (P=0.065), parental hip fracture (P=0.321), low body weight (P=0.279), current smoking (P=0.523), steroid use >3 months (P=0.098), alcohol > 14 units/week (P=0.537), and low calcium intake (P=0.969).

Falls history

Overall, 23.3% (31/133) of participants had a history of recurrent falls in the last year, with 8.3% (11/133) having two falls and a further 9% (12/133) ≥3 falls. Nearly one third (28.6%) reported having ever felt dizzy on standing up and 8% had a history of having a prior blackout. 25.9% of participants had orthostatic hypotension on erect and supine BP measurement.

Factors associated with recurrent falls in univariate regression analysis included older age (P=0.002). frailty (CFS, P=0.000), higher TUG (P=0.009), lower MMSE (P=0.014), greater number of medication (P=0.016) and higher CCI (P=0.012). However, no association was identified between history of falls and other risk factors for falls including: feeling dizzy on standing (P=0.111), past history of blackout (P=0.767), serum 25(OH)D (P=0.094), orthostatic hypotension (P=0.459). Additionally, those with a falls history were no more likely to have risk factors for fracture including: previous fracture (P=0.054), early menopause (P=0.058), low calcium intake (P=0.642), family history of osteoporosis (P=0.160), parental hip fracture (P=0.736), low body weight (P=0.619), height loss (P=0.498), late menarche (P=0.682), excess alcohol intake (more than 14 units per week) (P=0.380), current smoking (P=0.972) or steroid use for more than 3 months (P=0.208).

Early menopause

One of the most frequent risk factors identified was early menopause. Nearly half (42.7%, 53/124) of female participants reported menopause before the age of 45. Of those, only three patients reported taking Hormone Replacement Therapy (HRT) which included one patient on HRT during the study. The mean age of menopause was 44.5±4.9 years (reported in only 61 participants) and ranged from 28 to 53 years. Mean age of menarche (n=64) was 13.3±1.5 years and ranged from 9 to 17 years. In a subgroup of people (n=39) where data was available for both menarche and menopause, mean duration of reproduction years was 31.3 ±4.7 (range 22-40). There was no difference in age (P=0.543), frailty (P=0.140), CCI (P=0.567) or number of medications (P=0.541) in those with early menopause.

There was also no significant association between early menopause and history of previous fracture (P=0.101), DXA diagnosis (P=0.853) or previous osteoporosis treatment (P=0.647). Additionally, those with early menopause were no more likely to have other risk factors for osteoporosis including: family history (P=0.696), low body weight (P=0.143), parental hip fracture (P=0.394), steroid use (P=0.695), alcohol >14 units a week (P=0.100) or lower calcium intake (P=0.06).

Other risk factors

Other risk factors for osteoporosis and fracture that were assessed in the cohort are listed in table 19 above. Mean dietary calcium intake (excluding supplements) at the first visit was 760mg/day, though 39% (52/133) of patients were taking calcium supplements at the time of the fracture. A third (33.1%, 44/133) of patients had reported height loss while a similar proportion had a family history of osteoporosis (30%, 40/133) with 11.3% (15/133) reporting a parental hip fracture. Almost a quarter (24%, 32/133) had a low body weight at the time of assessment, 17% (24/133) were smokers and 13.5% (18/133) reported drinking > 14 units of alcohol per week. 18.7% (25/133) reported intermittent steroid use with four patients having long term use (>3 months).

Treatment history

The majority of participants, 84.9% (113/133) were eligible for DXA (by ISCD criteria) prior to their fracture yet, of these, only 43% (58/113) had it done (13). Overall, 12.8% (29/133) reported previous treatment for osteoporosis. Of these, six had been on more than one treatment for osteoporosis and the majority (24/29) had bisphosphonates including alendronate (16), risedronate (3), ibandronate (1) and zoledronic acid (4). A further nine patients had been treated with denosumab and two had previously been treated with recombinant parathyroid hormone (preotact), though one did not complete the course. One patient was treated with risedronate followed by rPTH and another rPTH followed by risedronate. Three were treated with bisphosphonates (two with alendronate and one with risedronate) followed by denosumab and one patient had denosumab followed by zoledronate. Of these, 18 were on antiresorptive therapy at the time of the fracture. six denosumab, two zoledronate and ten alendronate. Two of those who had discontinued denosumab did not have any therapy at the time of cessation.

4.3.7 Other clinical measurements

Table 21: Biophysical measures for the prospective wrist fracture cohort

Biophysical measure (n)	**Mean ± SD (%)**
TUG, seconds (n=109) TUG >10 seconds	11.5 ± 8.5 64 (58.7%)
Dominant hand grip, kg (n=71)	19.0 ±7.0
Non dominant hand grip, kg (n=60)	17.0±7.0
Creatinine, umol/l) (n=133) (> 84umol/l, upper limit of normal)	69.9 ±17.7 25.0 (18.8%)
Corrected calcium, mmol//l (n=133)	2.41 ± 0.14
PTH, pg/ml (n=119) >65	47.18 ± 27.18 22 (18.4%)
Vitamin D, nmol/l (n=122) <30 30-49.9 ≥50	71.5 ± 31.7 8 (6.6%) 23 (18.9%) 91 (74.6%)
Bone turnover markers (n=119) CTX (ng/ml) Osteocalcin (ng/ml) PINP (ng/ml) Total alkaline phosphatase (IU/l)	 0.40 ± 0.20 23.70 ± 11.20 68.50±40.50 89.1 ± 41.1

Mean TUG at first visit was 11.4 seconds. Of the 109 participants who completed the test, 58.7% (64) took more than 10 seconds. Only five patients who completed the test had a result greater than 20 seconds.

Mean hand grip strength in the dominant hand was 19.0 ±7.0 kg whereas in the non-dominant hand it was 17.0±7.0 kg. Dominant hand grip strength was significantly different in women with a fracture of dominant wrist (n=11) and without a fracture (n=54) (11.0±4.9kg vs 19.2±6.0kg, p=0.000). Non-dominant hand grip strength was not significantly different between the women who had a non-dominant wrist fracture (n=11) and those without (n=45) (14.4 ± 10.3kg vs 17.5 ±5.9kg, p=0.354). For men, the numbers were very small. Dominant hand grip strength was significantly different in one man with a dominant wrist fracture and 5 without (18kg vs 30.3±4.4kg, p=0.042). Non-dominant grip strength was assessed in one man with a non-dominant wrist fracture and 3 without (20kg vs 28.3±1.5kg, p=0.062). 18.5% (23/124) women did not have any grip strength measurement. 18.8% (19/101) women had grip strength <16kg. Only one man had grip strength <27kg of the nine assessed. (258)

One quarter of the participants had an abnormal renal profile (Creatinine >84umol/l). The majority (91.7%) had serum 25OHD tested, and of those only 6.6% were deficient (<30nmol/l) with a further 18.9% insufficient (30-49.9nmol/l). Overall, 74.6% of patients had replete vitamin D status (>50nmol/l) and 16.3% had biochemical evidence of hyperparathyroidism (PTH >65.0 pg/ml). BTM results were available for the majority of the cohort (119/133). Mean CTX was above the therapeutic range (0.40±0.20 ng/ml) as was mean P1NP (68.50±40.50 ng/ml) and osteocalcin (23.70 ± 11.20 ng/ml).

A number of additional blood tests were taken as part of screening for secondary causes of osteoporosis. A very small proportion (6%, 8/133) of patients had a monoclonal band identified after testing with serum electrophoresis and two others had minor abnormalities. Coeliac screen (TTG) was negative for all patients. LFT's were abnormal in 12% (16/133) with one requiring a referral to hepatology. Thirteen patients had a TSH above the upper limit of normal (>4.2 U/L) and in four it was below (<0.27mU/L). Hyperthyroidism was also evident on repeat testing in two cases and referrals were organised to endocrinology. Of women with FBC results available, 14.5% (18/123) had anaemia (Hb < 11.5 g/dl) and six of the nine men also were anaemic (Hb < 13.5 g/dl).

Diagnosis by DXA

Table 22: DXA results for participants in prospective wrist fracture cohort

Site of assessment	Number of patients (%)
Diagnosis by central DXA (n=130)	
Normal BMD	14 (10.8%)
Osteopaenia	63 (48.5%)
Osteoporosis	54 (40.8%)
T score AP spine (n=126)	-1.6 ± 1.4
>-1.0	38 (30.2%)
-1.0 to -2.5	50 (39.7%)
<-2.5	38 (30.2%)
T score femoral neck (n=125)	-1.7±1.0
>-1.0	21 (16.8%)
-1.0 to -2.5	71 (56.8%)
<-2.5	33 (26.4%)
T score total hip (n=128)	-1.4 ± 1.2
>-1.0	44 (34.4%)
-1.0 to -2.5	61 (47.7%)
<-2.5	24 (18.0%)
T score distal 1/3 forearm (n=98)	-2.1±1.7
> -1.0	26 (26.5%)
-1.0 to < -2.5	35 (35.7%)
<-2.5	37 (37.8%)
AP spine BMD (g/cm^2)	0.868 ± 0.155
Femoral neck BMD (g/cm^2)	0.657 ± 0.115
Total hip BMD (g/cm^2)	0.771 ± 0.147
1/3 forearm BMD (g/cm^2)	0.566 ± 0.103

DXA was performed on 132 patients though BMD was not measured at all sites. As shown in table 22 above, using central DXA (spine or hip sites) we identified that 41.5% of patients had osteoporosis, 47.7% had osteopaenia and 10.8% had normal BMD.

At the AP spine, 30.2% had scores in the osteoporotic range, 39.7% osteopaenic and 30.2% normal whereas at the total hip, 18% were osteoporotic, 47.7% osteopaenic and 34.4% normal. At the femoral neck corresponding values were: 26.4% osteoporotic, 56.8% osteopaenic and 16.8% normal. The site with the highest proportion of patients with osteoporotic scores was the distal forearm where it affected 37.5% with a further 35.7% osteopaenic and 26.5% normal here. In two patients, the forearm sites was the only site available for DXA assessment. When forearm sites were

also included in the diagnosis, 56.1% (74/132) had osteoporosis, 36.1% (48/132) osteopaenia and 7.6% (10/132) had normal BMD. Overall, mean T scores were: AP spine -1.6, femoral neck -1.7, total hip -1.4,and 1/3 forearm -2.2.

US heel was also performed in 34.5% (46/133) of the participants. Of these, 23.9% (11/46) had a normal score, 18.8% (25/46) had T scores between -1.0 to <-2.5 e and 21.7% (10/46) had T scores <-2.5. The mean T scores on US -1.7 $\pm$0.9.

Table 23: Characteristics of patients in the wrist fracture cohort categorised by DXA diagnosis (spine and hip sites)

Characteristic	Normal	Osteopaenia	Osteoporosis	P value
Age	67.3±9.6	68.5±9.9	67.6±12.0	
>70	5 (35.7%)	26 (41.9%)	25 (46.2%)	0.685
Sex				
Female	12 (85.7%)	56 (90.4%)	53 (98.1%)	0.131
Male	2 (14.3%)	6 (9.5%)	1 (1.9%)	
Charlson Comorbidity Index				
1-2	5 (35.7%)	25 (39.7%)	18 (33.3%)	0.771
3-4	6 (42.9%)	30 (48.4%)	25 (46.3%)	
≥5	3 (21.5%)	8 (12.9%)	11 (20.4%)	
Number of medications				
<5	10 (71.4%)	37 (59.7%)	32 (59.3%)	0.687
Clinical Frailty Scale				
Frail	1 (7.1%)	4 (6.7%)	14 (26.9%)	0.010
Living alone	4 (28.6%)	17 (27%)	13 (24.1%)	0.564
Mean TUG (seconds)	10.5 ± 2.5	10.0 ± 3.7	13.7 ± 12.8	0.095
Grip strength (kg)				
Dominant (n=70)	22.3 ± 5.4	19.5 ± 7.8	16.9 ± 6.4	0.088
Non dominant (n=59)	21.4 ± 5.2	19.1±6.1	13.6 ± 7.8	0.005
Serum PTH (ng/ml)	48.8 ± 17	43.7 ± 17	51.9 ± 37	0.376
>65 ng/ml	2 (14.3%)	11 (19.3%)	9 (19.1%)	0.905
Serum 25(OH)D (nmol/l)	67 ± 22	72 ± 32	71 ± 33	0.883
CTX (ng/ml)	0.327 ±15	0.423 ± 24	0.382±.21	0.328
OC (ng/ml)	22.0 ± 9.7	26.0 ± 12.2	22 ± 10.0	0.170
PINP (ng/ml)	59±32	71±33	68.0 ± 50.0	0.529
T score AP spine (n=126)				
>-1	14 (100%)	18 (30.5%)	6 (11.3%)	0.000
-1—2.5	0	41 (69.5%)	9 (17%)	
<-2.5	NA	NA	38 (71.7%)	
T score total hip (n=128)				
>-1	14 (100%)	25 (41.7%)	5 (9.3%)	0.000
-1 to <-2.5	0	35 (58.3%)	26 (48.1%)	
<-2.5	NA	NA	23 (42.6%)	
T score femoral neck (n=126)				
>-1	13 (100%)	8 (13.8%)	0 (0%)	0.000
-1—2.5	0 (0%)	50 (86.2%)	21 (38.9%)	
<-2.5	NA	NA	33 (61.5%)	
T score 1/3 Forearm (n=96)				
>-1	10 (38.5%)	14 (53.8 %)	2 (7.7%)	0.000
-1 to < -2.5	3 (8.6%)	19 (54.3%)	13 (37.1%)	
<-2.5	0	15 (41.7%)	21 (58.3%)	

Table 24: Characteristics of patients in the wrist fracture cohort categorised by DXA diagnosis (Continued)

Characteristic	Normal	Osteopaenia	Osteoporosis	P value
QUS heel (45)				
>-1	2 (40.0%)	7 (28.0%)	1 (6.7%)	0.303
--1.0 to <- 2.5	3 (60.0%)	13 (52.0%)	9 (60.0%)	
<-2.5	0	5 (20.0%)	5 (33.3%)	
Risk Factors				
Previous fracture (n=130)	6 (42.9%)	25 (40.3%)	31 (57.4%)	0.172
Early menopause (n=121)	6 (42.9%)	25 (42.4%)	21 (43%)	0.990
Family history (n=125)	3 (21.4%)	21 (33.9%)	16 (32.7%)	0.661
Parental hip fracture (n=125)	1 (7.1%)	8 (12.9%)	6 (12.2%)	0.834
Low body weight * (n=124)	2 (14.3%)	11 (17.7%)	18 (37.4%)	0.037
Alcohol (>14units/week) (n=122)	11(78.6%)	53 (86.9%)	40 (85.1%)	0.751
Current smoking (n=122)	4 (28.6%)	10 (16.4%)	10 (21.3%)	0.485
Calcium <700mg/day (n=114)	2 (14.3%)	30 (51.7%)	20 (47.6%)	0.039

**Low body weight =BMI<18.5kg/m²*

Table 23 and 24 summarise the characteristics of the cohort by central DXA diagnosis (normal BMD, osteopaenia or osteoporosis). There were no significant differences for most characteristics by diagnosis including for age, sex, TUG CCI, number of medications, previous fracture, early menopause, family history, parental hip fracture, alcohol intake >14 units per week, vitamin D levels or BTM markers.

However, patients with osteoporosis were more likely to be frail (26.7%) compared to 6.7-7.1% in those with osteopaenia or normal BMD (P=0.010). In fact, of those with a CFS indicating frailty (>4), 76.7% had central DXA T scores in the osteoporotic range. Additionally, osteoporotic patients were twice as likely to have a low body weight (37.4% vs 14.3 - 17.7 %, P=0.037). Non-dominant grip strength was also lower in those with osteoporosis (13.6 ± 7.8 kg) versus osteopaenic (19.1 ± 6.1kg) or normal BMD (21.4 ± 5.2kg) (P=0.005). Notably, low dietary calcium intake (<700 mg/day, excluding supplements) was about three times more common in those with osteopaenia/ osteoporosis vs normal BMD vs (47.6 - 51.7 vs 14.3 %, P=0.039). In further analyses, dietary calcium intake was also shown to be positively correlated with FN BMD (P=0.005) but not other sites.

Site specific T scores are also outlined by diagnoses in table 23. Concordance rate with overall diagnosis of osteoporosis was greatest in the spine (71.7%), followed by the neck of femur (61.5%) and then the forearm (58.3%).

We also compared for differences in the characteristics of patients with T scores in the osteoporotic range versus normal or osteopaenia at the forearm. Those over 70 years of age were twice as likely to have osteoporosis at the forearm (T score <-2.5) than younger participants (64.9% vs 31.1%,

P=0.002). It was also more likely in those who were frail (25.0% vs 5.0%, P=0.008%), had low body weight (40.0 vs 11.0%, P=0.002), higher CCI (>4) (30.0 vs 8.0% P=0.001) and polypharmacy (56.0 v 26.0%, P=0.003). However, there was no association with sex (P=0.400) or risk factors including early menopause (P=0.393), family history of osteoporosis (P=0.371), parental hip fracture (P=0.530), current smoking (P=0.765), alcohol > 14 units per week (P=0.486), or low calcium intake (P=0.173).

Antiosteoporosis medication

Table 25: Characteristics of patients categorised by anti-osteoporosis treatment

Characteristic	**Treatment*** **n= 29**	**No treatment** **n=104**	**P-value**
Age (years)	73.6 ± 10.3	67.5 ± 10.6	0.001
Sex			
Female	28 (96.6%)	96 (92.3%)	0.375
Male	1 (3.4%)	8 (7.7%)	
CCI			
1-2	2 (6.9%)	45 (43.3%)	0.001
2-4	18 (62.1%)	45 (43.3%)	
>4	9 (31%)	14 (13.5%)	
CFS			
Non frail	19 (67.9%)	90 (89.1%)	0.015
Frail	9 (32.1%)	11 (10.9%)	
Number of medications			
<5	15 (51.7%)	74 (71.2%)	0.073
>5	14 (48.3%)	50 (28.8%)	
Recurrent falls			
Yes	10 (35.7%)	21 (20.2%)	0.126
No	18 (64.5%)	83 (79.8%)	
MMSE >24	4 (26.7%)	7 (13.2%)	0.243
DXA diagnosis			
Normal	1 (3.4%)	13 (12.9%)	0.003
Osteopaenia	8 (27.6%)	54 (53.5%)	
Osteoporosis	20 (69.0%)	34 (33.7%)	
Previous fracture	21 (72.4%)	41 (39.4%)	0.003
AP spine BMD	0.816 ± 0.120 (n=27)	0.882±.16 (n=98)	0.048
FN BMD	0.626 ± 0.100 (n=29)	0.666±.0.120 (n=96)	0.101
TH BMD	0.702±.13 (n=28)	0.790 ± 0.150 (n=98)	0.005
1/3 Forearm BMD	0.519±.07 (12)	0.571± 0.10 (n=86)	0.101
CTX (ng/ml)	0.238 ±. 0.220	0.440±.21	0.000
OC (ng/ml)	14.8 ± 11	23.0 ± 12.0	0.007
PINP (ng/ml)	42.0 ± 27.0	76.0 ± 40.0	0.000
Serum 25(OH)D (nmol/l)	87 ± 28	66 ± 31	0.002

*CCI: Charlson Comorbidity Index, CFS: Clinical Frailty Scale, MMSE Mini Mental State Examination DXA: Dual-energy X-ray Absorptiometry FN BMD Femoral neck Bone Mineral Density, TH BMD Total hip Bone Mineral Density *Osteoporosis treatment includes antiresorptive or anabolic therapies*

Those who had received prior or current treatment for osteoporosis were more likely to have osteoporosis by standard DXA criteria (69.0% vs 33.7% P=0.003). On further analysis, the prevalence of a diagnosis of osteoporosis was also greater in those on treatment when using a forearm T score (89.7 vs 46.6% P=0.000). Those on treatment were also older (73.6 vs 67.5 years, P=0.001), had a higher prevalence of prior fracture (72.4 vs 39.4%, P=0.003) and low body weight (48.0 vs 19.6%, P=0.008) and had higher CCI (P=0.001). Most notably, they were three times more likely to be frail (32.1 vs 10.9 % P=0.015). Those who had treatment versus no treatment also had lower BMD at the spine (0.812 vs 0.882 g/cm^2, P=0.038) and total hip (0.702 vs 0.790 g/cm^2, P=0.004). While patients also had lower BMD at other sites (neck of femur and distal forearm), this was not statistically significant. Not surprisingly BTM were lower in patients with a history of treatment including CTX (0.238 vs 0.440 ng/ml, P=0.000), PINP (76.0 vs 42.0 ng/ml, P=0.000) and osteocalcin (14.8 vs 23.0 ng/ml, P =0.007). Conversely, vitamin D levels were significantly higher (87 vs 66 nmol/l, P=0.002). There was no difference in sex (P=0.100) or MMSE scores (p=0.243).

4.4 Discussion

4.4.1 Patient characteristics

We identified that in our prospective cohort of patients with distal forearm fractures, 93% were female and the mean age was 69.3±11.0 years. A similar high ratio of female to male was reported an Irish study (259) and a recent Icelandic study (260). Overall, fracture rates have been reported at more than five times higher in women than in men aged over 50 and there is a proportionately greater incidence of forearm fracture in older females (aged over 65) compared to other fragility fractures (261). Recent studies have shown incidence of wrist fractures increasing with age and then stabilising in women (>80) while the fracture incidence in men starts to rise >80 (262). Less than half (46.6%) had a dominant hand fracture similar to other studies (263). A quarter of the participants (27%) lived alone at the time of the fracture, which has previously been associated with wrist fracture (264). Two thirds of the group had a CCI >2 and the prevalence of polypharmacy was 39.8%, though ten (7.5%**)** were not taking any regular medication at the time of recruitment. In another reported study there was a similar CCI and and prevalence of polypharamcy though this cohort was older as patients younger than 60 were not recruited (265). Half of the participants declined cognitive assessment, though less than half (42.9%) of those that completed the test achieved a score of 24 or greater. This is higher than the rates of cognitive impairment reported in other studies. Cognitive impairment (including assessment by MMSE<24) has been shown to be a risk factor for injurious falls and specifically for wrist fractures (266).

About one quarter of the participants were frail (as measured by CFS). There are very limited studies available examining the association between frailty and wrist fractures. One very small recent study of wrist fracture patients (n=27) identified that 7% were frail and 70% prefrail using the Fried Frailty Index (267). To our knowledge, this is the first study reporting the CFS for patients with wrist fractures. Of the 109 participants that completed the TUG, 58.7% (64) took more than 10 seconds including five patients who completed the test in more than 20 seconds. The TUG is a well-known measure of functional mobility. TUG was shown in a cohort of over 1800 participants of TILDA to be a useful screening tool for frailty using a cut-off of 10 seconds. This cut off identified a group including 93% of the frail population and excluding 62% of the not frail population (identified using with Fried criteria) (268). TUG is also associated with falls risk and can predict falls and therefore has the potential to identify patients who might benefit from falls risk reduction interventions (269). Almost one in five women and one of the nine men had abnormal grip strength in our study (270). Those with osteoporosis had lower non dominant grip strength which could represent "osteosarcopenia". Other studies have shown higher rates of sarcopenia in patients with wrist fractures (incidence 27.9%-31.7%) and poorer functional outcomes in thus group (157).

Recurrent falls

Recurrent falls were reported by almost a quarter of patients. A similar proportion (25.9%) had orthostatic hypotension based on standard criteria. A recent systematic review calculated the prevalence of OH in community dwelling older adults to be 22.2% (271). Orthostatic hypotension was also associated with risk of future fracture including higher risk of wrist fracture (OR 1.87, CI 1.19-2.95) in more than 3000 Irish adults age >50 in the TILDA study (272). A similar association has been shown in other recent studies (273). Additonally, almost a third of our participants reported symptoms of OH. While most patients reported that their fall was a result of a slip or a trip, OH may have been a contributing aetiological factor. This is a modifiable risk factor and given its relatively high prevalence highlights its importance as part of a comprehensive falls risk assessment after fragility wrist fracture.

Risk factors for fractures

Almost half of our participants (45.9%) reported having had a previous fracture, 17 (12.8%) having had vertebral fractures and 13 (9.8%) reported more than one previous fracture. This is a higher burden of prevalent vertebral fracture(s) and historical fractures than was reported in our cohort in chapter 2. However, this does include all fracture types, not just hip and vertebral. Early menopause (<45 years of age) was reported by 42.7% of women in this study whereas it is typically identified in about 5-10% of western populations (274). In one Irish cohort (n=100) of women with fragility wrist fracture, early menopause was reported in 76% of study participants (158). However, this study excluded patients who had a prior diagnosis or treatment for osteoporosis and probably increased the proportion of women who fractured at a younger age due secondary osteoporosis due to premature menopause. In a large study in the US (n=6616), females with surgical versus natural menopause had a higher rate of incident wrist fracture (9.3 vs 7.8 %,P<0.05) at 21 years follow up (275). However, many of the women in our study did not remember their age of menopause and those who had early menopause were more likely to be smokers which of itself is an independent risk factor for fracture (276).

Mean dietary calcium intake in our study was 754mg/day with almost 40% of participants reporting a low intake (<700 mg/day). In our study there was no relationship between dietary calcium intake and age. In NANS (n=226) average intake for women was 985mg and men 908mg (54). However, a number of cohort studies have shown considerably lower self-reported calcium intake in older adults. In the TUDA cohort study, it was reported that overall, only 3.5% of patients were meeting the recommended daily dairy requirement (55). In TILDA, a nationally representative cohort study, 70% of older adults did not consume the recommended three portions of calcium rich foods (56). We also found that those with osteopaenia/ osteoporosis were three times more likely to have low intake. Dietary calcium intake in our study was also shown to be positively correlated with femoral neck BMD (P=0.005) but not other sites. In general, low calcium intake can contribute to secondary hyperparathyroidism which is associated with cortical bone loss at neck of femur and potentially at distal forearm. Dietary calcium intake has been shown to be a risk factor for wrist and distal forearm

fracture, particularly in men (143). A recently published systematic review showed that increasing dietary intake does increase BMD at all sites though magnitude of this increase was small (277)

Low body weight (defined as BMI <18.5kg/m^2), reported in one quarter of our participants, has been shown to be a frequent risk factor in patients with wrist fracture (278). Furthermore, 17% were smokers and 13.5% reported consuming in excess of 14 units of alcohol per week (279).

Diagnosis of osteoporosis

The prevalence of osteoporosis in the cohort was 41.5% and when using forearm T score a further 11.3% of participants had T scores <-2.5. The participants with osteoporosis were more likely to be frail, have lower grip strength, BMI and lower calcium intake. As discussed in earlier chapters, reported prevalence of osteoporosis varies between 17-68% (see chapter 1) though most report a similar proportion. In our study, in chapter 2, we found a 57.9% prevalence of osteoporosis which is on the higher end of what is generally reported. However, unlike this cohort which only included patients with a recent wrist fracture. the latter study had patients referred by GPs who were potentially more likely to have a more complex medical history and lower T scores which likely accounts for the overall higher prevalence of osteoporosis. Most of the patients in the study had forearm BMD assessed and in 37.8% of cases T scores were in the osteoporotic range. In addition to this, concordance rate with overall diagnosis of osteoporosis (using both standard sites) was greatest in the spine (71.7%) followed by the neck of femur (61.5%) and then the forearm (58.3%). In the cohort of men examined in the Mr F study with distal radius fracture the same significantly lower regional BMD was reported (145).

4.4.2 Improvements resulting from this research

This study identifies the number and characteristics of patients presenting to St James's Hospital with fragility fractures of the wrist. Prior to this study, only HIPE data was used for fracture identification, while now additional fractures are identified using NIMIS allowing the capture of all outpatient wrist fractures. This has resulted in a significant expansion of FLS within St James's hospital.

We report valuable information that can help in future planning of the Fracture Liaison Service (FLS). We identified a high rate of non-attendance. Unlike many studies, distal forearm fractures are often described in younger fitter women whereas in our cohort a significant proportion of patients were frail and older - consideration should be given to this when planning appointment times, location, duration and physical access to DXA. This data may help guide the development of FLS locally and nationally.

Though the numbers in our study are relatively small, it highlights the importance of bone health assessment and treatment in patients with risk factors, both in primary and secondary prevention. Only one in five patients had treatment with anti-osteoporosis medications prior to presenting with a wrist fracture. Given the risk factor profile of the cohort and the high rate of previous fracture this suggests a significant 'treatment gap'. Outside of bone health considerations, the study highlights other important factors related to falls risk. In particular, the high prevalence of orthostatic hypotension suggests its should be incoporated into falls risk assessment in FLS.

4.4.3 Strengths

This is the first study of its type to describe in detail the characteristics of patients with distal forearm fracture in Ireland. The data was collected at separate visits from routine clinical care at the orthopaedic fracture clinic and patients were all seen soon after their fracture to reduce recall bias. Furthermore, significant efforts were made to facilitate the inclusion of older frailer adults and patients with functional limitation due to their fracture. For example, the study was conducted in the bone health clinic located on the ground floor of an accessible building, well serviced by public transport, and with very flexible time slots. Appointments were also agreed over the phone, reminders sent when requested and missed appointments rescheduled up to three times. Several patient characteristics were examined that are not frequently reported in other studies: frailty, timed up and go, grip strength of the unfractured wrist, cognition, and lying and standing blood pressure measurements. US heel, forearm DXA, bone turnover markers and blood screening tests for secondary causes of osteoporosis were also assessed.

4.4.4 Limitations

There is missing data for some variables though overall this is low. The ultrasound machine had to be serviced during the study period resulting in some patients not being able to have QUS heel measurements. For some data, we relied on the patient's recollection of events (e.g. age of menarche and menopause, number of falls) which some were not able to recall and may introduce recall bias. While lying and standing blood pressure was recorded using a sphygmomanometer, the diagnosis of orthostatic hypotension as well as recovery and other features could be explored in more detail using other diagnostic techniques such as active stand using continuous beat-to-beat non-invasive blood pressure monitoring. As this study is specific to patients attending St James's hospital, findings in several areas may not be generalisable to the wider population and additionally all participants were Caucasian. Finally, I as the principal investigator carried out all of the assessments and so there could be unconscious researcher bias, though standardised tools and methods were used consistently throughout.

4.4.5 Conclusion

We reported a high prevalence of osteoporosis by DXA (41.5%) in patients with forearm fracure and a greater prevalence when also including forearm DXA. Our cohort included a significant proportion of patients with a history of previous fractures including vertebral fractures (45.9%) yet low treatment rates (12.8%) suggesting evidence of a significant treatment gap. Factors associated with a densitometric diagnosis of osteoporosis included frailty, low BMI, low dietary calcium intake and reduced grip strength. Further research could further explore the relationship between early menopause and wrist and other fractures. As we also reported a higher than expected prevalence of multimorbidity, polypharmacy and frailty, it may also be useful to explore the contribution of these factors to fracture risk and outcome as well as considering them in the design of services going forward. Furthermore, a quarter of our cohort had a significant postural drop in blood pressure on bedside assessment. Further research could explore this association in more detail. However, given the high prevalence and potentially modifiable risk it confers we suggest incorporating identification of orthostatic hypotension into routine assessment of patients following wrist fracture.

Chapter 5: Socio-economic outcomes and mortality in the first year after wrist fracture.

5.1 Introduction

Wrist fracture is one of the most common fracture types. In current literature, it is considered the fragility fracture that more commonly affects younger 'older' adults. However, it also occurs in recurrent fallers who could benefit from a falls assessment or in patients with undiagnosed osteoporosis who should be on treatment. Furthermore, the impact of distal forearm fracture in older adults who are frail or have cognitive impairment can be significant though they are often underrepresented or excluded from research studies. Regardless of age, wrist fractures may require hospital admission. It can impact people's ability to drive or work and may contribute to or necessitate a change in living circumstances for older adults if recovery is slow or incomplete.

The demographic and clinical features of the study group were described in chapter four. This chapter will describe some of the outcomes assessed. We aimed to capture the health care usage of patients in the cohort and changes in their medical care including changes in medications. In addition, we aimed to capture changes in their living circumstances and in their daily lives including the impact on driving and working. We also recorded falls, fracture and mortality outcomes for the group at one year.

5.2 Methods and materials

5.2.1 Patient selection and recruitment

Patients presenting to St James's Hospital following a wrist fracture were identified using the National Integrated Medical Imaging System (NIMIS) system and all were invited to participate. The inclusion and exclusion criteria are outlined in Chapter 4.

5.2.2 Data Collection

Baseline demographic and clinical characteristics were recorded at the initial visit as outlined in the chapter four.

Clinical outcome measures were assessed at three time points; the initial visit (ideally within 12 weeks), and at a scheduled six month assessment and twelve month assessment post fracture. The date and time of each assessment were recorded as well as the time since the fracture. Factors relating to the impact of the fracture on the patient were assessed in a detailed patient interview and also using validated outcome measures.

Non-attendance and cancellation

It was recorded If the patient did not attend their appointments.

Patient interview

At initial assessment, the ability to attend work and drive were recorded. It was also noted if the patient was admitted to the hospital following diagnosis of their fracture. Hospital admission details including length of stay and discharge destination were recorded and if additional supports were required at home at discharge. Discharge destinations were categorised as (1) returning home to own home, (2) returning home to own home with additional supports, (3) discharged to rehabilitation, (4) discharged to convalescence, (5) discharged to long term care (new admission), (6) discharged back to long term care. Length of stay was subcategorised into less than 3 days or greater than or equal to 3 days. Patient care, during the admission or arising from the fracture presentation were recorded, including if there was surgical or non-surgical management, inpatient rehabilitation, and changes to medication or diet as a result of bone health or falls prevention interventions. Medication adherence was investigated during the patient interview by patient self report at six and twelve months using the ABC taxonomy described by Vrijens et al (280):

A) initiation: when the patient takes the first dose of a prescribed medication

B) implementation: the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose, and

C) discontinuation: when the patient stops taking the prescribed medication, for whatever reason(s).

Hospital admissions during the follow-up period of one year were also examined. Variables recorded included length of stay and reason for admission. During the patient interviews at follow-up visits it was recorded if there subsequent falls or fractures. It was also recorded if the patient was due to have follow-up with the bone health or the orthopaedic service after one year or was referred to other services or had a significant new medical diagnosis e.g. stroke.

Clinical measurements

During the patient interview, the online CGEM calculator was used to estimate dietary calcium intake (254) (see appendix D) Grip strength was measured using the same Jamar dynamometer at each visit by standard technique as described in chapter four. The Timed Up and Go test was also assessed (255). Serum 25(OH)D was measured at each patient's first assessment as outlined in chapter four. If the patient had previously abnormal levels or changes in treatment serum 25(OH)D levels were repeated at follow up appointments. BTM were measured according to the technique outlined in chapter 4 at follow up appointments.

5.2.3 Data analysis

Data analysis was performed using SPSSv26. Numerical data was reported using means and standard deviations for normally distributed variables. or otherwise medians and IQRs. Parametric and nonparametric tests are used to explore relationships between variables. We first investigated admission following wrist fracture. Excluding patients who sustained a distal forearm fracture while admitted to the hospital for another reason, we calculated the admission rate (number admitted/number of patients presenting with fractures). We then explored the factors contributing to prolonged admission using Mann-Whitney U test and Chi-squared test. Changes in dietary calcium intake were explored using Friedman test.

5.3 Results

Table 26: Participant outcomes including blood test results and other measured outcomes at initial and 6 month and 12 month assessments

Characteristic	Initial	6 month	12 month
CTX (ng/ml) Full cohort All three visits (n=82)	 0.377 (n=119) 0.395±0.220	 0.252 (n=102) 0.251±0.170	 0.172 (n=112) 0.200±0.150
OC (ng/ml) Full cohort All three visits	 22.3 (n=118) 24.1±11	 17.5 (n=103) 21.2±12	 15.6 (n=111) 18.5±11
PINP (ng/ml) Full cohort All three visits	 63.7 (n=105) 67±32	 42.8 (n=105) 44.7±26.1	 34.9 (n=111) 35±21
Serum 25(OH)D (nmol/l)	71.5±31.7 (n=121)	74.0(IQR 44.5)(n=84)	77.7±23.3 (n=105)
PTH (pg/ml)	41.5 (n=119)	43.7 (n=102)	39.3 (n=111)
Calcium intake (mg/day) Full cohort All three visits (n=96)	 735.7±? (n=111) 728±299 (n=88)	 770±282 (n=64) 753±253 (n=50)	 771 ± ? (n=80) 789 ±253 (n=66)
Fractures (n)			4
Hospital admission (n)			26
Mortality (n)			4

5.3.1 Non attendance

Table 27: Attendance at prospective study appointments

Patient attendance	Number
Initial appointment	133
All appointments (on time)	96
Initial and only one follow-up (on time)	14
12 month follow up	112
One visit only	12

Due to lack of availability, not all patients were able to attend all three assessments. 34.6% (46/133) of patients did not attend more than one scheduled appointment during the study period. 100% (n=133) completed at least one assessment within six months and were therefore included in the study. 72.2% (96/133) attended all three visits within the recommended timeframes.

Time to first visit varied with 38.3% (51/133) seen in the first 6 weeks following fracture, 33.3% (45/133) between 6 and 12 weeks and 27.8% (37/133) after 12 weeks. For 16 of these patients, the initial assessment was conducted at 6 month as they were unable to attend prior to that time.

5.3.2 Admission to hospital

Hospital admission at the time of fracture presentation

Two patients were already in hospital at the time of fracture. Overall, 33.3% (44/130) of the remaining patients were admitted (including admission for surgical procedure). Excluding patients already in hospital and those admitted for a surgical procedure (LOS <3days), there were 18 other admissions. Total length of stay for these 18 patients was 1024 days, range 3-182, median 48 days, IQR 12.5-98. Further characteristics of these 18 patients and associations with admission are outlined in table 28.

Table 28: Characteristics of patients with long LOS (> 2 days) following wrist fracture (n=18)

Patient characteristics	**Median(IQR)**
Age (years)	85
CFS	Number
1	2
2	2
3	1
4	3
5	2
6	4
7	4
TUG (sec) (n=10)	14.1 (11.3-16)
CCI	4
Number of regular medications	9.5 (4.2-1.3)
Independent pADLS prior to injury	9
Discharge destination	
New LTC	4
Moved in with family	1
Home with increased support	6

CFS: Clinical Frailty Scale, TUG: Timed up and go test, CCI: Charlson Comorbidity Index, pADLs: Personal Activities of Daily Living, LTC: Long Term Care

Median age was 85 years. CFS was recorded for all patients and ranged from 1 to 7. Half (55.6%) were described as frail by the scale. TUG was assessed in 10 inpatients and median value was 14.1 seconds (IQR 11.3-16.5). Median CCI was 4 and median number of medications was 9.5, (IQR 4.75-11.25). Nine of the patients described themselves as independent with ADLs prior to the fracture.

Four were discharged to nursing homes having been admitted from home and six required increased home supports on discharge. One patient moved in with her niece on discharge having previously lived alone.

A number of associations were identified between patient characteristics and hospital admission. Patients admitted to hospital had a higher CCI (P=0.000), were older (P=0.000) more likely to have a previous diagnosis of hypertension (P=0.000) and be taking more medications (P=0.000). Specifically, those taking 5 or more medications versus <5 were more likely to be admitted to hospital (77.8% vs 34.5%, P=0.001). There was also a significant association between CFS and admission (P=0.000) with patients being more likely to be frail (55.6% v 9% p=0.000). Additionally, 50% reported requiring assistance with ADLs prior to their fracture versus 11% who were not admitted (P =0.000). Admitted patients were also more likely to have sustained another injury at the time of fracture (55% v 9.7%, P=0.000) and had a higher prevalence of prior vertebral fracture (18.3% v 2.6%, P= 0.042). Performance on the TUG was associated with hospitalisation (P=0.000) as was cognition as measured by thr MMSE (P=0.007).

Patients with lower BMD and T scores at hip and forearm sites were also more likely to be admitted including FN BMD (P=0.01), FN T score (P=0.01), total hip BMD (P=0.048), total hip T score (P=0.041), total forearm T score (P=0.045), and BMD (P=0.036). However, there was no significant association between 1/3 forearm BMD or T score, AP spine BMD or QUS T score. Patients with T scores in the osteoporotic range at the 1/3 forearm were not more likely to be admitted but on further analysis, if admitted they were more likely to have longer length of stay (LOS) (P=0.009). Median LOS for those with osteoporotic versus non-osteoporotic T scores was 84 days (IQR 51-143) versus 13 days (IQR 9-49).

No significant difference in several other characteristics of patients admitted verus non-admitted was identified including: genders, specific medical diagnoses: COPD/asthma, osteoarthritis, hyperlipidaemia, dementia, GORD and low body weight. There was no significant association with fracture characteristics including dominant hand fracture, surgery, mechanism of injury, or according to fracture risk factors: previous fracture, early menopause, age of menopause, age of menarche, reproductive years family history of osteoporosis, parental hip fracture, late menarche, recurrent falls, feeling dizzy when standing, having had a black out previously, postural drop on lying and standing BP measurement, excess alcohol, or dietary calcium intake. There was also no significant relationship observed between admission and blood test results including haemoglobin, creatinine, ALP, ESR, corrected calcium, phosphate, TSH, FT4, CTX, Osteocalcin, PTH or vitamin D with the exception of PINP (p=0.008).

Admission during the follow up period

New medical problems were reported by 48.2% of participants (54/112) at the 12 month follow up appointment. The details were accurately known for the following 42 patients as outlined below.

Table 29: New medical diagnoses within 12 months of wrist fracture

Medical problem	**Number of patients**
New fracture/incident fracture	4
Cancer	5
Pain (non-malignant)	7
Cognition impairment	3
Gastrointestinal	3
Mental health	2
Respiratory	5
Cardiovascular	5
Stroke	2
Other	6

Furthermore, 23% (26/112) patients were admitted in the year following wrist fracture (21 had one admission and 3 two admissions). One patient was admitted on four occasions and another five times.

Table 30: Reasons for admission in the first year after fracture

Reason for admission	**Number of patients**
COPD/respiratory sepsis	5
Cancer related	3
Pain (non-malignant)	3
Wrist related surgery	3
Acute coronary syndrome/heart failure	2
Fracture	2
Stroke	2
Possible GI bleeding	1
Bells palsy	1
Other infection	1
Other	7

Length of stay were available for re-admissions to St James's hospital (16 patients). Median length of stay was 16.5 days (IQR 7-59, range 2-169) and reason for this admission was available for all 26 patients as outlined in table 30. COPD, cancer or pain accounted for most admissions. Patients re-admitted were more likely to be frail (32% v 11%, P=0.018), have a higher CCI (P=0.013) and lower haemoglobin (P=0.017).

However, there was no significant association between re-admission and age, gender, medical diagnosis (COPD, hypertension, OA, hyperlipidaemia, dementia, GORD, osteoporosis) or polypharmacy. We also found no difference in other factors in patients who were re-admitted ncluding: functional independence prior to fracture, TUG, MMSE, fracture characteristics (dominant hand fracture, right wrist, surgical treatment of the fracture, having another injury at the same time of fracture) or fracture risk factors (previous fracture, family history of osteoporosis, parental hip fracture, previous vertebral fracture, low body weight, height loss, late menarche, age of menopause, reproductive years, steroid use, smoking, recurrent falls, OH, previous blackout, excess alcohol, calcium intake). DXA and QUS results were also not signficantly different.

5.3.3 Outcomes relating to impact of the fracture

Changes to work practices/time not working

Only ten of the study participants were in employment at the time of the fracture. Regarding changes in work, one patient changed job and two never returned to work. Two participants missed 7 weeks and a further two patients did not attend work for 3 months following the fracture. One patient took 3 weeks and another 6 weeks off work while the longest perod ou of work was 10 weeks.

Time not driving

Fifty patients (37.6%) had been driving prior to fracturing their wrist. However, data were available for only 30 patients regarding driving post fracture. Three patients decided not to drive at one year but intended to return and four decided not to drive again. Additionally, two patients were unsure how long they stopped driving for.

Table 31: Time not driving following wrist fracture

Weeks without driving	Number of patients
1	1
2	1
3	4
4	1
5	1
6	4
7	1
8	1
10	2
12	5

5.3.4 Management characteristics

25.9% (35/135 fractures) of participants had surgery. Patients who sustained other injuries at the time of wrist fracture were more likely to have surgery (52% v 21% P=0.009) and to have higher serum PTH at 6 months (P=0.035). Otherwise, no significant associations were found with regard to gender, age, medical diagnosis CCI, CFS, functional status, fracture characteristics, fracture risk factors, DXA or other blood results. There were also no significant associations identified between having surgery and adherence with antiosteoporosis medication, falls, fractures or future hospital admission at 6 or 12 months.

Bone health management

All patients were counselled regarding lifestyle and dietary factors to optimise their bone health. 41.3% (55/133) of patients were advised changes in their supplement use; 47 to commence a different supplementt and 8 to stop or reduce the dose ther current of calcium supplement.

Table 32: Recommended supplemental calcium and/or vitamin D following wrist fracture

Name of supplement	**Number of patients**
Cholecalciferol 25000 units (per month)	8
Cholecalciferol 800 units (daily)	12
Vitamin D as part of fosavance (daily)	3
Cadelius 600mg/1000units (daily)	13
Calcichew 500mg/400units (daily)	7
Kalcipos 500mg/800 units (daily)	1
Not specified	3

Two thirds (67.4%, 90/133) of patients were advised to commence an anti-osteoporosis medication based on clinical risk of fractures and in all cases this was an antiresorptive medication. Of these, 58.9% (53/90) were started on once weekly bisphosphonate with all but one patient being prescribed alendronate. A further 22.8% (20/90) were advised to start zolendronic acid (two did not receive it) and 18.9% (17/90) on denosumab. Twelve patients were advised to continue their current treatment (7 denosumab, 2 zoledronic and 3 oral bisphosphonate). In total, (76.7%, 102/133) were on antiresorptive treatment after their wrist fracture. Lastly, five were advised to stop alendronate and one declined all treatment options.

Changes in bone health and other measures at six and twelve months

Changes in exercise

At the initial assessment 88 patients reported completing some exercise each week. Most reported walking was as their main form of exercise: 52.2% (46/88) walking every day, 19.3% (17/88) less than three times a week, 13.6% (12/88) four times a week. 10.2% (9/88) five times a week and only two 6 times a week. Advice was given about exercise to optimise bone health to 114 patients. However, of these 21.1% (24/114) reported increased exercise on follow-up assessments.

Changes in calcium intake in diet

All patients were advised to optimse calcium intake in their diet. We recommended patients to consume more than 700mg of calcium from dietary sources preferably and to consider supplement use if intake was low. There was a significant increase in dietary calcium intake (n= 53) over the assessments. On average, dietary calcium intake increased from 661mg per day at baseline to 755 mg per day at one year, representing a 14.2% increment.

Changes in vitamin D level

There was no statistically significant difference between vitamin D levels at the initial assessment, or at 6 or 12 month follow up.. Mean vitamin D at baseline was 71.8 nmol/l, at six months 74.0 nmol/l and at 12 months 76.7 nmol/l. There was also no statistically significant difference between PTH levels at the initial visit or at six months though it was lower at 12 months (P=0.044).

Medication adherence

Initiation

One patient reported not starting the prescribed antiresportive medication due to forgetfulness at the six month review. However, all other patients took at least one dose.

Implementation

14.4% (13/90) reported taking less than 80% of their prescribed doses from the time of prescription to the 12 month review. When asked openly for reasons to account for this patients cited: dental concerns (3), GI bleeding under investigation (1), forgetting to take the tablets (6), issues with the cost of the medication (1) and lack of understanding why the medication was important (2).

Discontinuation

Following clinical assessment and shared decision making, 24.4% (22/90) had changes made to treatment recommendations at their six month review.

Change in bone turnover markers

Table 33: Bone turnover markers: change over one year follow after wrist fracture

	Initial	Six months	Twelve months
CTX (ng/ml)	0.376 (0.232 - 0.522) N=120	0.253 (0.106-0.383) N=101	0.172 (0.089-0.172) N=111
Osteocalcin (ng/ml)	22.1(15.2-29.9) N=119	17.6 (11.7-28.9) N=102	15.6 (11.2-24) N=111
PINP (ng/ml)	61.6 (42.3-85.7) N=119	43.3 (22.9-58.3) N=104	37.1 (18-50.4) N=111

** The number at each assessment varies and includes patients not on anti-resorptve therapy.*

Table 33 shows the number of patients with bone turnover markers (BTM) available from the initial assessment following wrist fracture and at 6 and 12 month assessments. Median CTX was 0.376 initially, 0.253ng/ml at six months and at 0.172ng/ml 12 months. A similar change was seen for Osteocalcin and PINP. Median osteocalcin was initially 22.1ng/ml at six months, 17.6 ng/ml and at 12 months 15.6ng/ml. The corresponding values for P1NP were 61.6ng/ml initially, 43.3ng/ml at six months and 37.1ng/ml.at one year. Overall, when comparing BTM at baseline to at 12 months, the following decreases were found: CTX (-54.2%), P1NP (-40.0%) and OC (- 29.4%).

Table 34: CTX monitoring on antiresorptive therapy

	Initial	6 months	12 months	P value
CTX (ng/ml) on antiresorptive therapy (n=54)	0.446±0.231	0.252±0.183	0.180±0.166	0.000
CTX (ng/ml) not on treatment (n=21)	0.347±0.146	0.297±0.114	0.289±0.126	0.185

There was also a significant difference in bone turnover markers (CTX) within 54 individuals who were on antiresorptive therapy and tested at all three time points. In contrast, when looking at the group not offered treatment there was no significant differences in CTX at either 6 or 12 month follow up. Overall, there was a 59.6% decline in CTX.

Referral to other services

In our unit the occupational therapy department run 'hand rehabilitation group therapy' which all patients are referred to following wrist fracture. Additionally, 23.3% (31/133) were referred to the physiotherapy service for falls intervention. 19.5% (26/133) were also referred to medical services that included gastroenterology (2), haematology (2), ENT for evaluation for surgery for hyperparathyroidism (2), and specialist pain services (2). One patient was also referred to each of immunology, cardiology, endocrinology, alpha 1 antitrypsin clinic and one back to the orthopaedic team.

5.3.5 Follow up at one year

Mortality, Falls and incident fracture

Four (3%) patients died during the study period. 31.3% (35/112) reported at least one further fall during the 12 months. Of these, 22.3% (25/112) had one fall, 7.1% (8/112) two falls two $\geq$ 3 falls. Four patients (3%) reported new fractures in the year post fracture.

Follow up after one year

16.5% (22/133) of patients were given a follow up appointment with the bone health service following the study period. The remainder of the patients were discharged to the care of their GPs and 7.5% (10/133) patients were continuing to attend the orthopaedic team.

5.4 Discussion

This study examined several factors related to the impact of sustaining a distal forearm fracture over the age of fifty in Ireland. The recent SCOPE report highlighted that the number of new fragility fractures in Ireland in 2019 had increased compared to 2010, equivalent to an increment from 6.1 to 20.6 fractures per 1000 in 2019. Age is an important risk factor for fracture and in Ireland the population aged 50 years or more is projected to increase by 38% between 2019 and 2034. As wrist fractures are one of the most common fragility fractures the impact of these fracture is important (6).

5.4.1 Hospital admission and health care utilisation

A number of factors determine if a patient is admitted following a fracture. Firstly, a patient may be admitted if they require surgical fixation. This may be a day case or a short hospital stay depending on the logistics of arranging surgery in particular units. Longer hospital admission can be due to other injuries sustained, the nature of the injuries and illness or complications associated with the injury. In some cases functional decline and collapse or unavailability of the carer network are important. The admission rate following wrist fracture in our hospital was 33%. Excluding admission solely for surgery (largely performed as day-cases), 13.5% of the cohort were admitted immediately following the fracture. There are some studies looking at rates of admission in other countries which include 9% in Sweden (199), 12-14% in Italy (200) and 26.2-28.5% in Australia (201). The patients in our study accounted for 1024 bed days. Estimates of the cost of patient care in an acute hospital for one day in Ireland in 2020 was €878 while costs of day-case and other admission types vary (281). Therefore, including only the patients whose LOS exceeded 2 days, acute hospital care at the time of fracture for the participants of this study is estimated to have cost €899,072. In Ireland, wrist fractures accounted for 2000 admissions and 12000 acute bed days a year from 2004 to 2014 (204). Using the same estimate, 12,000 acute bed days cost approximately €10,536,000. This data was compiled using the Inpatient Management System. Furthermore, this study reported there was an increase in 6% in the number of patients admitted and an increase of 87% and 10% in the number of male and female acute bed days from 2004 to 2014 (204).

We also recorded if patients were admitted in the first year following a fracture . An American study published in 2010 reported an increase of 19.9% in admissions in the 6 months following a fracture (203). Total mean healthcare costs in the first year after distal forearm fracture were estimated at £1,680 in the USA in 2003 (282), £1,460 in Sweden in 2004 (283) and £1,151 in the Netherlands in 2008 (284) and €6905 in France in 2022 (significantly lower than €23,925 for hip, €10,319 for clinical vertebral or €10,319 for proximal humerus fractures (285). The only study comparing healthcare

costs to an age/sex-matched control group reported median incremental costs of £330 for women and £496 for men in Canada in 2006 (286).

5.4.2 Change in living circumstances

Eleven patients in the study reported a change of living circumstances following the injury and hospital admission including four moving to long-term care and six requiring increased home supports to facilitate discharge home. One patient left their home to move in with family having previously lived alone. There is little research available on the rates of institutional care admission following wrist fracture or the need for additional supports following loss of functional independence due to fracture. One recently published study showed that 3.24% of patients who had DRF surgery were transferred from the acute hospital to post-acute care (287). An older study examined over two thousand patients with forearm fractures in Germany and showed no difference in living situation (288). Though it is important to note that in the methodology of this study if the patient had cognitive impairment or was in poor health they were not given the opportunity to participate. In the femoral fracture group in that study, a caregiver was given the opportunity to participate on behalf of the patient but they deemed this not necessary in the forearm group. The mean age of participants was 67.6 years, younger than in our study. It is likely that due to this methodology the patients who may have required a change of living circumstance would not have been captured.

5.4.3 Acute fracture management: surgical vs non-surgical

The rate of surgical fixation was 25.9% in our cohort. A recent systematic review concluded that in adults aged over 60 there was no improvement in medium term outcomes, though there was in those who were younger. It also found that there was no significant difference in complication rates between groups (289).

5.4.4 Bone health management

All patients recruited in our study were seen by the FLS. As in other similar services, we found non-attendance and cancellation were frequent (34.6%). At a recent FLS workshop (290), speakers described up to 50% non-attendance rate at clinics. Our non-attendance rate was high despite many efforts being made to issue repeat appointments and offer flexible times and days. All patients recruited had DXA and bone health and falls assessment and the recommendations were recorded. Adherence with anti-osteoporosis medication is a challenge in osteoporosis management. Patients who attended had the results of their DXA, as well as education on osteoporosis and the benefits and risks of treatment. At six and twelve months, they had contact details for the clinical nurse specialists in the Bone Health Unit if they had questions or concerns. Our adherence rates with osteoporosis therapy were higher than in a recently published Irish study (75). In fact, in our cohort, 85.6% were taking the prescribed medication more than 80% of the time at their 12 month follow up appointment. We also reported bone turnover markers for those who were treated and identfied

that they were supressed by up to 50%, consistent with high persistence and adherence rates. We also examined the factors patients reported for poor adherence or persistence (including forgetfulness, cost, dental concern, GI bleeding, lack of understanding) and how using shared decision making may improve bone health management.

There was also a signifcant increase in self reported dietary calcium intake as estimated by our FFQ at 6 and 12 months post wrist fracture reflecting greater intake due to supplement use. Overall, the mean calcium intake our cohort was significantly higher than that reported in other Irish studies in the general population including TUDA (55) and TILDA (56). However, it was significantly lower than that reported in NANS (n=226) where average intake for women was 985mg and men 908mg (54).

5.4.5 Falls and fractures

In our study, at least a third reported the the fall causing the wrist fracture and at least one further fall in the follow-up period, despite having received a falls assessment after their fracture. Four patients (3%) also sustained further fractures within a year of fracturing their forearm. It is not surprising that participants had further fractures despite assessment and treatment for osteoporosis, as intervention measures can only reduce fracture risk. Indeed, this is identfied in several studies and this risk is highest soon after the index fractures (291). The relationship between BMD and refracture risk appears to be much higher with wrist fracture than other osteoporotic fractures (292). However, the numbers in this study are too small to further explore this, though the proportion of participants presenting with a subsequent fracture is lower than that seen in other studies. There were 9 subsequent fractures in a Japanese cohort of 141 published in 2015 (293). Hodsman et al reported in 2008 that the re-fracture rate after primary wrist fracture over ten years was 14.2%. While this is lower that the refracture rates seen for fractures at other sites like hip (24.9%), humerus (23.7%) and spine (25.7%), it is significantly higher than in those with no previous fracture (10.8%, $p<0.001$) (294). Similar longer term refracture rates have been reported in other studies (211) (212). Cuddihy et al showed the cumulative incidence of any subsequent fracture was 55% by 10 years and 80% by 20 years following the initial distal forearm fracture. They also showed an increased risk of vertebral fractures in all age categories and also hip fracture in women who sustained a wrist fracture after but not before the age of 70 (213). However, most other studies show an increased rate of hip fractures at all ages post wrist fractures (214, 215). The possible higher subsequent fracture rate in other studies may be explained by very low rates of anti-osteoporosis medication use in these cohorts. For example, 9% of patients with wrist fractures were taking anti-osteoporosis medication in Hodsman's study and 31% of those with previous fractures (294). Patients in our cohort may have benefited from the MDT interventions they received including falls risk and bone health assessments and interventions and onward referrals to therapists where indicated.

A recent study looked at 1057 patients with a DRF (85% women; mean age 70 years). Overall, 205 patients were treated prior to the introduction of an osteoporosis care program and 852 after. The

study reported subsequent fractures occurred in 27 patients (2.6%) with a mean interval of 29 months between surgery and incident fracture. However, the fracture rate was significantly lower in patients in the osteoporosis care program (1.9% vs. 5.4%, p = 0.004) with a relative risk reduction of 65% for all subsequent fractures and 86% for hip fractures (295).

5.4.6 Mortality

This is a relatively small group but it is important to note that of the 133 patients recruited, four (3%) had died at one year follow up. This number may under represent the true mortality following the fracture as a number of patients may had died between fracture diagnosis and recruitment or were not recruited as they had a terminal diagnosis or were receiving palliative care. A recent review looking at long term outcomes of patients following wrist fractures included 13 studies that reported data on mortality after wrist fracture and found that the risk of death in the first year was low (185). A recently published Canadian study considered 16,467 patients with wrist fractures aged over 65 as part of a bigger study and showed a one year mortality rate of 4.4%. This is much lower than the rates recorded for other fracture types; hip (24.6%), pelvis (18%), vertebral (17.9%) (296). In CaMOS, a prospective Canadian study including a younger cohort similar to that in our study aged over 50, the mortality rate following forearm fracture was 3.59 per 100 person years (1.99-3.37) with a hazard ration of 1.40 (1.04-1.87) adjusted for relevant confounders. A higher mortality risk was seen for women aged 75 and older (297). An Australian study showed that excess mortality following distal forearm was only in those sustaining subsequent fractures (298). More work and larger studies are needed to examine the impact of wrist fracture on mortality, in particular exploring the impact of the fracture on younger and older adults and in patients with other health conditions or more severe osteoporosis.

5.4.7 Limitations

This is a study of only white older adults with a large majority of female participants recruited following identification by a FLS within a hospital. It is a relatively small group from a single centre and may not be generalisable to a wider Irish or indeed other populations. As an observational study and it is subject to selection bias, whereby recruitment of patients may be affected by factors such as their ability to attend for follow up. However, every effort in our study was made to minimise bias through comprehensive patient identification, inviting all patients in a prompt time period after their fracture and organising appointments over the phone to choose the best times for participants to attend. We also offered repeat appointments, sometimes on multiple occasions and were flexibile if patients were unable to attend, facilitating clinics at other times if possible. Our site was on the ground floor and was also easily accessible by public transport. We also had 12 month outcomes for 87% of patients (112 attended the in-person 12 month follow up appointment).

However, we did not report detailed information regarding specific surgical procedures and radiological appearances or classifications. A minority of patients in the group underwent surgery and available evidence informs us that surgery versus conservative management does not appear

to impact functional outcomes in older adults. It is unlikely we would have sufficient numbers to draw meaningful conclusions regarding surgical techniques and the outcomes we were assessing. Howeer, we did record why patients were continuing to attend orthopaedic services or if they encountered any specific surgical complications.

There was also missing data and some data was not collected in the pre-specificied timeframe. However, we did not exclude frail functionally impaired older adults due to inability to attend, be it as a consequence of the fracture itself or their premorbid status.

5.4.8 Conclusion

This is the first study to our knowledge exploring the characteristics of Irish older adults requiring admission following wrist fractures. This research adds to the existing literature in Ireland regarding healthcare usage of patients with wrist fractures. As these fractures are an opportunity for intervention to prevent further fractures, the exploration of medication adherence from the patients' perspective is valuable. Furthermore, this work has highlighted some of the potential challenges and considerations in designing FLS and expanding at our unit and also nationally.

Chapter 6: Pain, function and health-related quality of life outcomes in the first year after wrist fracture.

6.1 Introduction

In 2018, the Blue Book standards were published for distal forearm fracture (DFF) care. There were also recommendations for how patients' outcomes should be monitored in the follow-up period after wrist fracture. In particular, attention was drawn to the fact that little research had been conducted to investigate patient outcomes or factors influencing these after distal forearm or wrist fractures (177). Patient reported outcome measures (PROMs) have become an essential measure of patient outcomes in healthcare. As part of the standardised reporting guidelines for wrist fracture, the importance of PROMs are highlighted (299). The most frequently used are the Patient Rated Wrist Evaluation (PRWE) and Disability of the Arm, Shoulder and Hand (DASH). These measure outcomes specific to wrist and upper limb function. More general measures such as VAS (Visual Analogue Scale) are also recommended though this is included as part of the PRWE. Another more general measure often used when assessing health outcomes is the Short Form 12 (SF12), reported as the Physical Component Score (PCS 12) and Mental Component Score (MCS 12).

The most important outcomes for patients after wrist fracture are pain and function. Traditionally, radiological outcomes were reported most frequently. However, in older adults, this does not correlate particularly well with functional outcome as they appear to tolerate larger deviations in x-ray appearance after fracture (175). More recently, after distal forearm fracture, it has been recommended that in clinical practice and research we strive to report patient reported outcomes. A recent review outlined the role of PROMs in distal forearm fracture care and the challenges in assessing for meaningful and clinically important differences. Comparison of PROMS at different timepoints after recovery has become incorporated into standard research practices (175).

The aim of our study was to examine the characteristics of patients following wrist fracture and to consider what factors influence patient and other reported outcomes, with particular regard to bone health measures such as BMD. We aimed to assess patient outcomes at (1) initial visit after the fracture, (2) six months and (3) 12 months so as to track how patients recover over time. We also aimed to explore for factors that may influence these outcomes post fracture including age, sex, frailty, comorbidity, affected side, previous fracture history, falls history, serum 25(OH)D, BMD, surgery and hospital admission for longer than two days.

6.2 Methods and materials

6.2.1 Participant appointments

All patients were seen at the initial assessment and again at follow up at 6 and 12 months. Baseline assessments were performed initially as outlined in chapter 4. Patient clinical management and admission data were collected and analysed as per chapter 5. At each of these time points further assessments were performed focusing on pain and functional outcomes at six and twelve months post their wrist fracture. A key focus of the assessment were the Patient Reported Outcome Measures (PROMs). In this study, validated and standardised measures were used as are discussed below (see copies of assessments included in appendix E, F, G).

6.2.2 Non-attendance and cancellation

In designing the study we were aware that a significant proportion of the participants would be older adults and may be frail, have limited mobility, multiple comorbidities and rely on the assistance of others. Our FLS has a high 'do not attend rate' of more than 50% as is seen in similar services nationally (300). Some of the most common reasons for non-attendance are frailty, living alone as well as lack of education (300). Therefore, we designed our study to reduce this in a far as is possible, so as to have more representative population inclusive of older adults. Appointment scheduling was flexible and initial appointments were intended to be conducted within 3 months of the fracture or as soon as the patient was available. This is in line with recommended timing of post fracture assessment as outlined in the IOF Capture the Fracture Best Practice Framework. Based on service KPIs services are awarded a level ranging from level 1-3 for each standard. For standard three (timing of post fracture assessment), it is recommended that patients are assessed within 8 weeks (level 3), 12 weeks (level 2) and 16 weeks (level 1) (301). In cases of non-attendance and cancellation, participants were contacted by phone and if they were still interested in attending were offered at least three appointments with different times. All appointments were conducted in a ground floor accessible clinic and relatives and carers were welcome where the patient indicated this was their preference.

6.2.3 Data collection

PROMs

The Twelve Item Short Form (SF12) was the first measure used. Patients complete each section using a Likert scale provided. Mental Component Scores and Physical Component Scores were then calculated using the orthotoolkit (302).

PROMs specific to wrist function were also assessed. Firstly, we used the Patient Rated Wrist Evaluation (PRWE) which consists of two sections and subscales for (1) pain and (2) functional assessment. The full questionnaire is included in appendix F. The sum of both sections gives a score between 0 and 100 with a higher score indicating poorer performance. For example, no pain and or

functional impairment would result in a score of zero. While generally comparisons of mean scores are used with reported PROMs following DRF, one study did report a Minimum Clinically Important Difference (MCID) of 11.5 points for the PRWE (303). The MCID represents a threshold value of change in PROM score deemed to have an implication in clinical management. The Disability of the Arm Shoulder and Hand questionnaire (DASH) was also used. It consists of a 30 questions regarding function of the upper limb and with total scores calculated as per guidelines. However, with the DASH, a score cannot be calculated if there are greater than three missing items. Higher scores are indicative of more perceived disability. While there are limitations with applying MCID for DASH, comparison of means or medians and IQR's remains the most common approach in research. Some studies have established the MCID for the DASH and reported it as 10.83, though it is important to note that this was not conducted in a wrist fracture cohort (299).

Timed up and Go (TUG)

Timed Up and Go (TUG) (255) was recorded where possible. This is a test where the time it takes for a patient to start from a seated position, walk three meters, turn around and return to the seated position in the same chair is measured. The timed up and go test was conducted at each visit where the patient was willing and able to participate. The same chair (with arms) was used for all patients and at every visit. The same measured area (3 metres) was also used. Patients were instructed to get up from a seated position in a chair and walk to the measured point, turn around and return to their seat and sit down again. They were given one practice walk first and timed on their second attempt. If patients were reluctant to participate due to fear of falling, pain or any other reason the test was not done.

Grip Strength

Grip strength was measured on all patients using the same Jamar dynamometer. The participant was asked if they would complete the test on both hands. For patients who did not want to do the test on their wrist fracture side due to pain, the non-fractured hand only was assessed. The same technique was used throughout all assessments (256). The Jamar Hand Dynamometer has a dual scale readout which displays isometric grip force from 0-90kg (0-200lb). It has a peak hold needle which automatically retains the highest reading until the device is reset. The second handle position was used for all participants. Hand dominance and side of fracture was recorded. The patient was assessed in a seated position with feet placed flat on the floor and the shoulder adducted, elbow flexed at ninety degrees and the forearm and wrist neutral. The device was placed in the palm of the hand with the handle resting on the middle of the four fingers. We checked that the instrument felt comfortable and that the needle was reset prior to asking the patient to squeeze the device. Patients were asked to squeeze as tightly and as for as long as possible, ensuring each squeeze was of at least five seconds duration. We ensured grip force was applied smoothly and three measurements were taken on each hand. The mean of three results was recorded in kg. Kim et al

examined patients treated by volar locking plate fixation for DRF and reported the minimum clinically important difference of grip strength to be 6.5 kg (304).

6.2.3 Statistical analysis

Statistical analysis was performed using SPSS v 26. Means and standard deviations were quoted for normally distributed variables and otherwise median and IQR were used. We examined for differences in patient characteristics between those whose first attendance was within the recommended time (ie < 12 weeks) versus > 12 weeks using Student's t-test and Chi-squared test. We also looked for any significant changes in PROM's in the first 6 months using Pearson or Spearman's correlation and Krsukal-Wallis test. We explored differences in outcomes between time points (baseline, 6 and 12 months). Changes in outcomes were analysed using the one way ANOVA, Kruskal-wallis test and the Friedman test as appropriate. We explored the relationship between patient outcomes and multiple factors including age, sex, frailty, comorbidity, affected side, previous fracture history, falls history, serum 25(OH)D, BMD, surgery and hospital admission for longer than two days. Spearmans and Pearson correlation, Chi-squared test, AMOVA, Kruskall-Wallis test and Friedman test were used where appropriate.

6.3 Results

6.3.1 Summary of patient participation

Table 35: Number of participants attending study appointments

Patient attendance	Number
Initial appointment	133
All appointments (on time)	96
Initial and only one follow-up (on time)	14
12 month follow up	112
One visit only	12

As discussed in chapter five, the majority of patients attended within 8-12 weeks as per the study protocol, and overall 117 attended their initial appointment within 5 months (see figure 11 below). The remaining 16 patients had their initial assessment 6 months after the fracture.

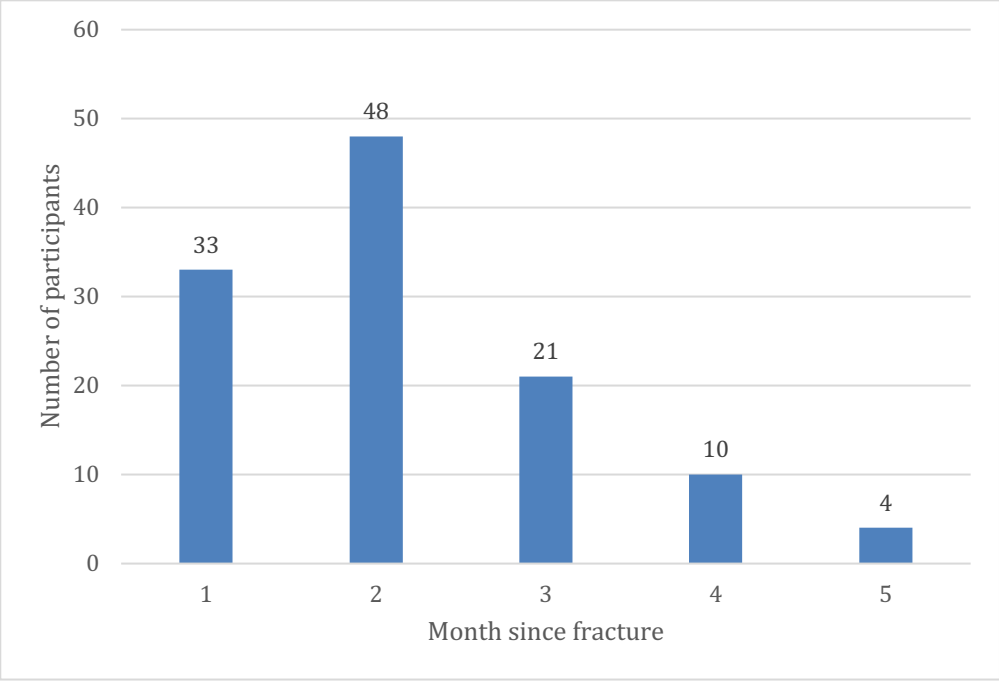


Figure 11: Number of participants who attended per month after fracture (within 1st six months)

6.3.2 Time to initial appointment and outcomes

Table 36: Characteristics of the participants categorised by time to first attendance

Characteristic	Attended within 12 weeks (n=96)	Attended after 12 weeks (n=37)	P value
Age (years)	69.4±11	69.4±11	0.985
Sex Female Male	 96 (94.2%) 7 (6.8%)	 28 (90.3%) 3 (9.7%)	 0.697
Normal BMD Osteopaenia Osteoporosis	10 (10%) 50 (50%) 40 (40%)	4 (12.9%) 13 (41.9%) 14 (45.2%)	0.719
Independent pADLS	89 (88.1%)	21 (67.7%)	0.013
Dominant hand	42 (41.6%)	19 (61.3%)	0.065
Other injury	15 (14.9%)	6 (20.0%)	0.572
Family history ofosteoporosis	26 (26.0%)	14 (50.0%)	0.021
Calcium intake (mg/day)	726 ±307	912±436	0.034
Frail (CFS >4)	11(11.0%)	9 (30.0%)	0.020
Very frail (CFS 6 or 7)	7 (7.0%)	8 (26.7%)	0.007
CCI ≥6	4(3.9%)	6 (19.4%)	0.010

BMD: Bone Mineral Density, pADLs: Personal Activities of Daily Living, CFS: Clinical Frailty Scale CCI: Charlson Comorbidity Index

We found that there was no difference in age, sex, DXA diagnosis or presence of other injury between those who attended their first appointment within or after 12 weeks. However, those who attended later were less likely to be independent with pADLs prior to fracture (67.7 vs 88.1 %, P=0.013) and three times more likely to be very frail (26.7 vs 7.0 %, P=0.02). They were also more likely to have a higher CCI ≥6 (19.4 vs 3.9% P=0.01), a family history of osteoporosis (50.0 vs 26.0%, P=0.021) and have higher daily dietary calcium intake (912 vs 726 mg /day, P=0.034).

SF12

There was a significant correlation between first PCS12 total scores and time to assessment indicating that the further the time from fracture the greater the PCS (Spearman correlation co-efficient (r= 0.191 P=0.046). However, there was not a significant correlation between MCS12 at the first assessment and time to assessment. (Spearmans rho -0.057 p=0.552).

PRWE

There was a significant correlation between PRWE result and time to first assessment (Spearman's rho -0.343 p=0.000). There was also significant difference between PRWE scores across the first five months after fracture (N=111,P=0.001)

Table 37: Variation in PRWE per month (within 6 month period) after wrist fracture

Month since fracture	Number of participants	Median	IQR
1	31	53.5	38.5
2	47	57	36.5
3	20	27.3	52.9
4	9	36.5	46.4
5	4	7.5	30.1

DASH

There is a significant negatiive correlation between time to first assessment and DASH result at first assessment (Spearman's rho -0.344 p=0.001). There was also a significant association between the month after fracture assessment and the DASH result (n =96, P=0.010).

Table 38: Variation in DASH per month (within 6 month period) after wrist fracture

Month since fracture	Number of participants	Median	IQR
1	27	61.2	31.9
2	42	64.2	34.8
3	17	40.2	61.7
4	6	48	54.5
5	4	9.5	17.4

6.3.3 Summary of TUG and grip strength in the 12 months following fracture

Table 39: Handgrip strength and Timed Up & Go at initial, 6 and 12 months assessments after wrist fracture

Characteristic	Initial	6 month	12 month
TUG (secs)			
Full cohort	9.4 (7.2-11.6**)** (n=109)	9.3 (2.2-16.4**)** (n=81)	9.1 (7.3-10.9) (n=80)
Attended all visits	11.2 ± 7.1 (n=87)	9.9 ± 2.9 (n=71)	10 ± 3.2 (n=69)
Measured at all three	10.7 ± 3.4 (n=52)	9.8 ± 2.6 (n=52)	9.8 ± 2.5 (n=52)
Dominant hand grip (kg)			
Dominant hand fracture	11 (5.5-16.5) (n=12)	14 (10-18) (n=40)	18 (13.5-22.5) (n=49)
Non-dominant hand fracture	20 (15-25) (n=59)	18 (14-22) (n=52)	20 (15-25) (n=59)
Non dominant hand grip (kg)			
Dominant hand fracture	18 (14-22) (n=48)	18 (14.5-21.5) (n=43)	18 (5.5-20.5) (n=48)
Non-dominant hand fracture	13.5 (4-23) (n=12)	15 (11-19) (n=50)	17 (12-22)(n=59)

Where variables were normally distributed mean ±SD is quoted otherwise, median (interquartile range) is quoted.

TUG

Median TUG was 9.4 seconds at initial assessment with no significant change at six months (9.3 seconds) or at one year (9.1 second). In participants where results were available at all three timepoints (n=52), there was also no significant change (P=0.23) indicating no apparent loss of physical function.

Grip strength

As shown in table 39, there was a significant improvement in grip strength in the fractured dominant hand throughout the first year. In the overall sample, grip strength improved in the non-dominant hand fracture side from 11 kg at baseline to 14kg at 6 months (P=0.026) with a further increase to 18 kg at one year (P=0.002). We did not show any significant improvement in grip strength in the fractured non-dominant hand or in non-fractured hands. In addition, we showed that at each time point, dominant hand grip strength was significantly lower in the fractured dominant hand than in those who had not had a fracture (11 vs 20kg, P=0.000, 15 vs 19kg, P=0.000, and 16 vs 20kg P=0.001 respectively) whereas in the nondominant hand the only statistically significant difference in strength between the fractured and non-fractured participants was observed at six months (15 vs 18.5kg, P=0.002).

6.3.6 Summary of PROMs in the first year

Table 40: Patient reported outcomes at initial, 6 and 12 months assesements after wrist fracture.

Characteristic	Initial	6 month	12 month
MCS12	46.7±10.6 (n=115)	54.3 (48.7-59.9)(n=103)	53.4 (46.9-59.9) (n=109)
PCS12	37.4±10.5 (n=114)	44.0(36.5-51.5) (n=103)	49.0 (39.3-58.7) (n=109)
PRWE **Pain subset***	47.1±28.5 (n=115)	8.5 (0-21) (n=104)	5.0 (0-12.3) (n=108) No pain 56 (n=111)
DASH	56 (36.2-75.9) (n=99)	15.5 (0-30.2) (n=93)	6.9 (0-18.2) (n=93)

**Pain subset includes the first five items of the PRWE.*

Where variables were normally distributed mean ± SD is quoted, otherwise median (interquartile range) is quoted.

Table 41: Patient reported outcomes for participants who had valid results at all three assessments

Characteristic	Initial	6 month	12 month	P value
MCS 12 (n=82)	46.9±10.2	51.7±10.7	52.0±10.1	0.002
PCS 12 (n=82)	37.1±9.4	44.6±9.2	46.1±10.9	0.000
PRWE (n=83)	52±24.7	19.2±24.1	15.5±22.7	0.000
DASH (n=63)	52.6 ± 24.3	18.6 ± 18.7	13.5±17.8	0.000

Friedman test performed for each variable for all timepoints

Summary of changes in PROMs

MCS 12

There was a 16.2% improvement in median MCS12 comparing initial assessment (46.7) to 6 months (54.3) (P= 0.002). However, at 12 months there was no further improvement. When specifically considering the same individuals who had assessments at all three timepoints, the mean MCS12 also improved by 9.8% from 46.9 to 51.7 (P=0.005) between the baseline and six months. Similarly, at 12 months, there was little further change in score (52.0) (p=0.639).

PCS 12

Overall, there was a 17.6% improvement in median PCS 12 between initial assessment (37.1) and six months (44.6). A further improvement of 11.3% was shown between six and twelve months (P=0.000). More specifically, the same 82 patients completed the SF12 at the all three timepoints with an overall improvement of 24.3% (p=0.000). In these participants PCS12 improved from 37.1 to 44.6 between baseline and six months (P=0.000) representing a 24.3% increased but there was no further change at twelve months (P=0.212).

PRWE

Overall, the mean PRWE was initially 47.1 with an 82% improvement identified at six months and a further improvement at 12 months. In individuals who had assessments at all three timepoints (n=83), PRWE scores were initially 52, decreasing to 19.2 at six months (P=0.000) representing a 32.8% improvement. Furthermore, at twelve months there was a further 19.2% improvement P=0.000). Additionally, at 12 months, half of patients (56/111) with a valid PRWE assessment were pain-free. The average PRWE for the entire cohort was lower (median 5) than for those who attended all three visits (mean 15.5). This may in part be accounted for my the wide IQR and SD around these averages but possibly also attendance bias, that those who were experiencing more pain and disability wree more likely to attend all appointments.

DASH

Overall, the median DASH was initially 56 and decreased to 15.5 at six months representing a 72% improvement. At 12 months there was also a further 59% improvement with it decreasing to 6.9. When considering the patients who had valid data at all timepoints (n=63), there was a significant improvementt in DASH (P=0.000) from 52.6 initially to 18.6 at six months and 13.5 at 12 months. Additionally, at twelve months only 5 patients had a DASH score of 0 indicating no disability.

As shown in table 40, the numbers of participants at each of the assessments were different. Due to limitations in the individual measures, in particular the DASH and other factors discussed later, fewer patients have results available for all three time points. However, as demonstrated when comparing the changes across all timepoints in the same individuals versus the entire study population the findings are similar.

6.4.7 Relationship between patient characteristics and PROMs

Table 42 summarises the relationships between different factors, including most proposed by Babatunde et al (305) and the assessment times. These factors were all associated with poorer outcomes.

Table 42: Factors associated with patient reported outcomes at different time points following wrist fracture

	PCS12	MCS12	DASH	PRWE
Older age	First assessment 6 months (+)		6 months (+)	
Female			6 months	
Comorbidities	6 months 12 months			
Frailty (CFS)	6 months 12 months		6 months 12 months	
Polypharmacy (≥5)	6 months 12 months		First assessment 6 months 12 months	
Spine BMD **Femoral neck BMD**		12 months	6 months 6 months 12 months	6 months 12 months
Fragility fracture (previous)			12 months	
BMI (<18.5 kg/m^2)				12 months
Recurrent falls ^	First assessment 12 months	12 months	6 months	
Parental hip fracture			First assessment	First assessment
Serum (25(OH)D)$^+$	12 months	First assessment	First assessment	
Dominant hand	First assessment 6 months	First assessment	First assessment 6 months 12 months	First assessment 6 months 12 months
Surgical treatment				
Prolonged hospital admission*	First assessment 6 months		First assessment 6 months	12 months

*^ Recurrent falls was defined as ≥2 falls in a 12 month period $^+$Higher vitamin D levels associated with poorer outcomes *Prolonged hospital admission was defined in our study as a hospital stay >2 days*

Age

Age correlated positively with DASH at six months (n=93, Spearman's rho 0.258, P=0.012, and and PCS 12 initially (n =114, Pearson -0.233, p-0.013,) and at six months (n=103, Spearman's rho -0.242, P=0.014). As age increased the DASH result was higher indicted more disability. Similarly in older age, PCS12 was lower indicatiing poorer physical health. However, age did not correlate with DASH or PRWE at any other timepoints.

Sex

Males versus females had lower DASH scores at 6 months (12.3 vs females 15.9, P=0.026) though no other differences were identified.

Comorbidities

Participants with a higher baseline CCI had a lower PCS 12 score at six months (P=0.022) and twelve months (P=0.019). However, no significant relationship was found between higher CCI (CCI>4) and wrist specific outcomes (PRWE and DASH).

BMD

We explored for correlations between PRWE, DASH, MCS 12 and PCS12 at all time points (initially and at 6 and 12 months) and BMD at the spine, femoral neck and total femur. There was a significant correlation between AP spine BMD and (1) PRWE at six months (n=125, Spearmans rho -0.274, P=0.006) and 12 months (n=103, Spearmans rho -0.194, P=0.043) (2) DASH at 6 months (n=89, Pearsons -0.251, P=0.018) and (3) MCS12 at 12 months (n=104, Pearsons -0.226, P=0.021). There was also a significant correlation between femoral neck BMD and (1) PRWE at 12 months (Spearman's rho -0.262 P=0.008) (2) DASH at 6 months (n=87, Pearson -0.244 P=0.023) and 12 months (Spearmans rho -0.251, P=0.018). No other significant correlations with BMD were identified.

Relationship between BMD and changes in PROMs

We also explored for correlations between changes in PRWE, DASH, MCS 12 and PCS12 between the (1) initial assessment and 6 months, (2) 6 to 12 months and (3) baseline to 12 months and BMD at the spine, femoral neck, total femur and forearm. There was a significant correlation between femoral neck BMD and changes between 6 and 12 months in PRWE (n= 87, spearmans rho 0.21, P=0.044) and DASH (n=74, spearman's rho 0.236, P=0.043). In addition, from six to twelve months changes in MCS12 were correlated to forearm BMD (n-71, spearman's rho -0.241, P=0.043). No other significant correlations with PROM changes were identified.

Other Factors and Outcomes

Patients with previous fractures had a poorer one year outcomes with regard to disability (DASH, P=0.023) while low body weight (BMI<18.5) was associated with more pain and disability as measured by PRWE at 12 months (P=0.012). Patients in this study who reported early menopause were more likely to have higher PRWE at 6 months (P=0.009) and PRWE (P=0.006) and DASH at 12 months (P=0.023). They also had significantly less improvement in function as shown by DASH at up to 12 months. Patients who reported recurrent falls (at baseline) were also shown to have poorer outcomes on initial MCS12 (P=0.003) and PCS 12 (P=0.030), DASH at 6 months (P=0.044) and at 12 months (P= 0.025). Parental hip fracture was associated with poorer outcomes in the DASH and PRWE at initial assessment (P=0.034, p=0.0.022) but there were no significant associations on SF12 or with any measure at later timepoints.

Frailty

There was a significant relationship between baseline frailty phenotype and better physical performance as assessed by PCS at six months (n=203, P=0.000) and 12 months (n=109, P=0.002). See figures 12-15 below outlining results of Kruskall-Wallis tests.

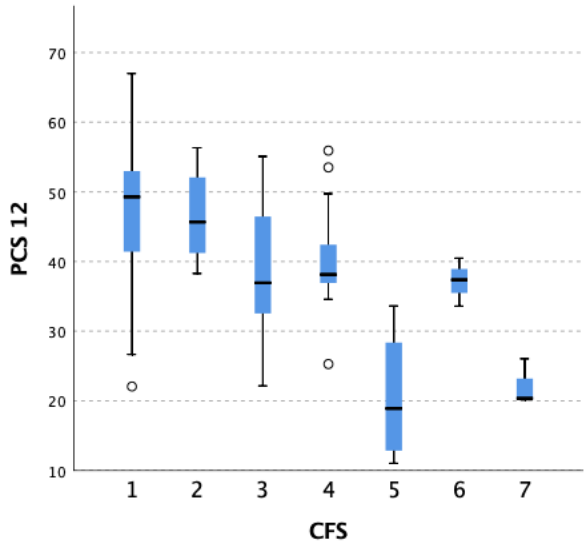


Figure 12: Physical Componenet Score at 6 months categorised by frailty status Score at 6 months categorised by frailty status

PCS12: Physical Component Score calculated from SF12 CFS: Clinical Frailty Scale

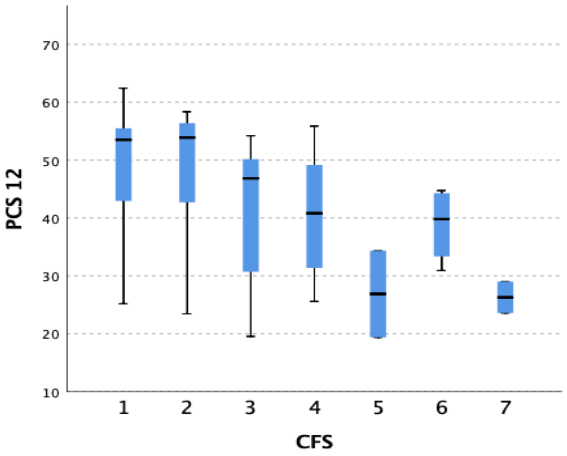


Figure 13: Physical Component Score at 12 months, categorised by frailty status

PCS12: Physical Component Score calculated from SF12 : CFS: Clinical Frailty Scale

There was also a significant relationship between increasing frailty and more upper limb disability (as measured by DASH) at 6 months (n=93, P=0.001) and 12 months (n=93, P=0.031).

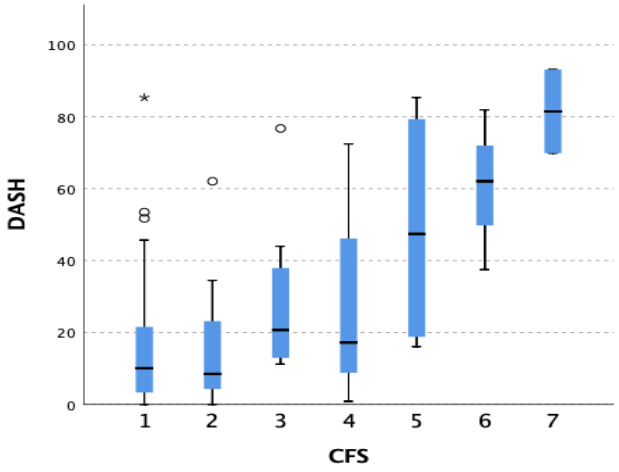


Figure 14: DASH score at 6 months categorised by frailty status

DASH: Disability of the Arm, Shoulder and Hand, CFS: Clinical Frailty Scale

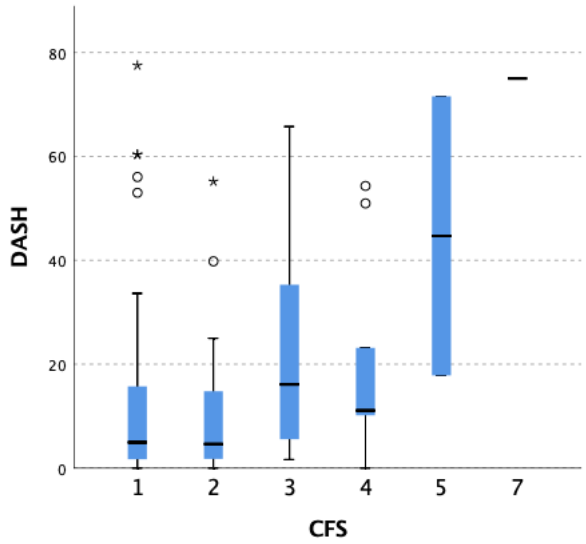


Figure 15: DASH score at 12 months categorised by frailty status

DASH Disability of the Arm, Shoulder and Hand CFS Clinical Frailty Scale

Polypharmacy

Polypharmacy (≥5 medications) was associated with more upper limb disability as assessed by DASH at initial presentation (P=0.001), six months (P=0.004) and twelve months (P=0.012). Patients with polypharmacy were also more likely to have lower physical function (PCS12) at 6 There were no other significant associations between polypharmacy and outcomes.

Dominant versus non dominant

Dominant hand fracture was associated with poorer outcomes on initial assessment with regard to physical function (PCS12, P= 0.041), mental health (MCS 12, P=0.001), upper limb disability (DASH, P=0.000) and pain (PRWE, P=0.000). These poorer outcomes were sustained at six months for physical function (PCS12, P=0.012) disability (DASH, P=0.013) and pain and function (PRWE, P=0.004). At 12 months, these patients also had an increased likelihood of pain and disability as measured by PRWE (P=0.025) and disability as measured by DASH (P=0.001). For example, in those with dominant versus non-dominant hand fracture, median PRWE at 12 months was 10.0 vs 1.7 (P=0.000).

Surgery

There was no significant difference in outcomes as assessed by PROM's at any time point between patients who had or did not have surgery.

Prolonged admission

Hospital admission in the cohort was discussed in detail in chapter 5. PROMS at all timepoints of patients with a nonsurgical admission for their wrist fracture was compared by length of stay (>2 days). Patient outcomes were also examined for those requiring longer, non-surgical admissions at the time of the fracture. Despite small numbers, those with a longer length of stay had a lower PCS12 (P=0.036) and higher DASH (P=0.019) initially and also lower PCS12 (P=0.001) and higher DASH (P=0.024) at six months and at 12 months lower PCS12 (P=0.003) and higher PRWE (P=0.049) indicating greater disability. Patients requiring admission for longer than 2 days also had less improvement in PRWE in the year following wrist fracture (P=0.002).

Vitamin D

There were significant positive correlations between baseline serum vitamin D level and greater disability (DASH) on initial assessment (P=0.045, R =0.208). Higher vitamin D was also associated with poorer outcomes as assessed by MCS 12 initially (P=0.049) and PCS 12 at 12 months (P=0.043).

6.4 Discussion

This prospective cohort of approximately 100 patients with a fragility fracture of the distal forearm identified improvements in several patient outcomes up to one year afterwards including in pain and function, as well as grip strength. The cohort included mostly women with a mean age of 69 years. Almost one in five had a Charlson comorbidity index of more than 4 and 15% had frailty. Over a third of the participants reported polypharmacy and 40% had densitometric osteoporosis.

6.4.1 Pain and disability

The most problematic outcomes following distal forearm fracture are pain and reduced function. Half (50.4%) of our cohort reported ongoing pain at 12 months and, only 5.4% had no disability. The proportion of patients with ongoing pain more than 6 months after a forearm fracture varied between 7.5% and 62% in a recently published systematic review (305). This systematic review examined 78 cohort studies (700,000 patients) that examined the longer term (6 months or beyond) outcomes of patients following wrist fracture. Previous cohort studies examining patient outcomes also use the SF12, PRWE and DASH most frequently. The mean and median baseline PROMS and the pattern of improvement in pain and disability were similar in our study to those recorded in studies included in this review (305). We showed most improvement in symptoms and function occurred in the first six months. Additionally, we observed continued smaller degrees of improvement between six months and one year. These findings are similar to other studies where most improvement occurred by six months and with little further gains thereafter up to periods of up to 4 years later (306). Similarly, our study showed the negative impact of wrist fracture on quality of life (measured by SF12 including PCS12 and MCS12), most striking in the early months after fracture. This is also highlighted elsewhere (307) (308). Further exploration of the trajectory and predictors of recovery may help to inform health care strategies to optimise outcomes post wrist fracture.

6.4.2 Factors associated with poorer patient outcomes

Age and sex

Older age was associated with poorer physical health as reported by participants on SF12. There was also an impact on wrist specific function at six months. Female sex was also associated with poorer wrist related function as measured by DASH at six months. Babatunde et al reported consistent finding across a number of studies showing the relationship between increasing age and female gender and poorer outcomes (305). Similarly in another smaller study, poorer outcomes were associated with being older, female and also lower socioeconomic status (309).

BMD

While the link between lower BMD and risk of wrist fracture is well established, associations between lower BMD and outcomes post wrist fracture have only been investigated in a few studies. We found that lower BMD at both the spine and the femoral neck were negatively correlated with outcomes. Spine BMD was associated with poorer outcomes at six months on DASH and MCS12 and at 6 and 12 months on the PRWE. Femoral neck BMD was associated with poorer outcomes on DASH at both 6 and 12 month assessments. However, there was no adjustment in this analysis for age or other factors which could be confounders. In few studies, BMD has been shown to be associated with clinical outcomes. For example, BMD was a better predictor of clinical outcome than radiographical features in one small (n=40) study (310). BMD was also associated with outcome as assessed by DASH in women treated operatively in another small (n=64) study in 2012 (311). However, some studies have not demonstrated any association. Indeed, in one study there was no association shown between DASH at one year and BMD (n=54) (312) and also in a recent study looking at 133 men after wrist fracture (313). The poorer outcomes regarding self-reported pain and disability could be due to the impact of low BMD on healing and alignment. One study showed that with lower T scores, there was an increasing likelihood of early instability, late carpal malalignment, and malunion (314). This may be in part an explanation. However, other studies have shown an association between BMD and radiographical features of severity (315). We do not have data on fracture alignment or radiographical features for our cohort. Furthermore, low BMD can be associated with low BMI and frailty which we have not adjusted for these in our analysis.

Affected side (dominant or non-dominant)

We showed a consistent association between the fracture site (dominant or non-dominant) and several outcomes. Patients who fractured their dominant hand, had poorer outcomes as measured by all three patient report outcome measures. Patients with dominant hand fractures had poorer outcomes on the wrist specific measures (PRWE and DASH) at all time points. This association has been shown in other studies (316). Patients with dominant hand fractures in our study also had a more significant change in grip strength. A recent study reported a 7kg difference in grip strength between patients with dominant hand fractures treated operatively and conservatively in the first three months (317). This was not seen in the non-dominant fracture group, similar to our cohort, suggesting a mechanism for more functional impairment in this group. A study that looked at younger patients (mean age 62) with longer follow up (mean follow up 42 months), showed no association with dominant hand fracture (318). This suggests that the most disparity in outcome between affected sides is seen soon after the injury.

Frailty

To our knowledge, this is the first study looking at the relationship between frailty (using a specific frailty measure) and wrist fracture outcome. Patients with higher CFS score had poorer outcomes as measured by PCS 12 and DASH at 6 and 12 months. A large prospective cohort study published in

2020 looked at 680 patients at baseline and 6 months and also at functional decline and associated factors (265). That cohort was older and had a lower rate of polypharmacy that our participants but had a similar burden of comorbidity. It showed that about one third of the patients recruited experienced a functional decline at six months. Additonally, functional decline was also more frequent in patients with comorbidity ($P < 0.0001$), polypharmacy ($P < 0.0001$), low health-related quality of life prior to the fall ($P < 0.0001$) and lower educational level ($P = 0.009$). This suggested that findings may be accounted for by patients being frailer, though there was no specifc specific frailty measure.

Hospital admission

Patients who had long hospital admissions (>2 days) also had have poorer outcomes across a number of measures including PCS 12 initially and at six months, DASH initially and at six months and PRWE at 12 months. Other studies have shown an association with needing to attend an emergency department after the fracture and poorer outcomes (305). However, hospital admission at the time of fracture and its association with outcome has not been examined in other studies. In our cohort, those admitted for longer than 2 days were older, more frail, had more comorbidities and were taking more medications that the participants not admitted. The differences are explored in detail in chapter 5. These factors may be part of the explanation for the poorer outcomes in these patients. There is also growing evidence of the impact of hospital admission on frail older adults. A recent literature recent highlights the higher rate of complications and poorer outcomes in older adults with frailty (319).

Polypharmacy

Polypharmacy was associated with poorer outcomes as measured by DASH at all time points and on PCS 12 at 6 and 12 months after fracture. This relationship has been explored in other studies (320). A retrospective cohort study showed that potentially inappropriate medication use hindered the improvement in activities of daily living and increased the incidence of subsequent falls in patients assessed (321).

Previous fracture and recurrent falls

Previous fragility fracture was shown in our cohort to be associated with poorer outcome as measured by DASH at 12 months. Similarly, recurrent falls are associated with poorer outcome in out cohort as measured by PCS12 initially and PCS12, MCS12 and DASH at 12 months. This has been shown in other studies to consistently impact outcome (305, 322).

Vitamin D

Higher vitamin D levels were associated with poorer functional outcomes and quality of life in our cohort (including lower MCS 12 and DASH at initial assessment and PCS 12 at twelve months). However, the association was not consistent over all measures or time points and sample sizes were small. It is possible that patients with higher vitamin D were on vitamin D supplements as they may have already had a diagnosis of osteoporosis or fractures or were frailer. Very few studies have been conducted looking at the association between vitamin D and wrist fracture outcomes. One recent study looked a fracture severity in terms of AO classification in 122 women and found that articular vs non-articular non-comminuted DRFs were associated with lower serum 25-hydroxyvitamin-D levels (323). In the first published RCT looking at the role of vitamin D in fracture healing, early bolus supplementation of vitamin D3 after a distal radius fracture did not result in enhanced fracture healing as assessed using HR-pQCT nor did it mprove patient reported outcomes. Remarkably, a decreased trabecular number and compression stiffness and also an increase in the serum marker of bone resorption (CTX) was observed in the high vitamin D3 dose group compared with the control group (324). However, this study was small and there were a number of limitations including a lack of BMD testing and subsequently a large variation in osteoporosis rates between the control and intervention group. Vitamin D deficiency is associated with secondary hyperparathyroidism which causes bone loss at cortical sites and therefore would be expected to affect forearm BMD more, with lower levels potentially having a negative impact.

Surgery and therapy

Surgery was not associated with any of the assessed patient outcomes in our study. However, all patients were referred to an 'OT hand group' so this could be a factor. The impact of interventions in hand therapy in DRF outcomes were reviewed in a Cochrane review in 2015 and showed that the available evidence from RCTs is insufficient to establish the relative effectiveness of the various interventions used in the rehabilitation of adults with fractures of the distal radius (325). Of note, the studies reviewed mostly excluded older adults. Chen et al published a meta-analysis exploring the evidence for surgical versus non-surgical management of patients over the age of 60 with wrist fractures (including 2 RCT's and 6 retrospective studies) and found no difference in PROMs though improvement in grip strength (326).

6.4.3 Strengths

This is the largest study of its type in Ireland to prospectively examine patients aged over 50 with fragility fractures of the distal forearm. We assessed a range of patient characteristics including measures of frailty, BMD and several patient reported outcome measures reflecting disability, function and pain. The study design allowed for the capture of as many patients as possible and included late attenders and participants who had missed or cancelled multiple appointments - patients who we found were more likely to be frail and less functionally independent despite being

of similar age. Finally and Importantly, unlike many cohort studies of patients following wrist fracture, follow up is usually for shorter periods (< 6 months) compared to our research which spanned three assessments over one year. We investigated the associations of factors such as BMD, frailty and polypharmacy with functional outcomes that few studies have done.

6.4.4 Limitations

The study was conducted in a single centre where all patients were identified by the FLS, and had assessments and interventions (e.g. bone health treatments initiated and referred to OT). Findings with regard to outcomes may therefore not be generalisable given that FLS services are poorly established in many hospitals in Ireland. In our study, due to non-attendance by some patients at follow up clinics there is missing prospective data which could bias our findings. However, every effort was made to facilitate patient follow up and we reported outcome data for 87% of the cohort at one year. Additionally, due to fatigue or frailty, some assessments could not be completed such as grip strength. Furthermore, there are specific requirements for scoring some outcome measures. For example, the DASH questionnaire is invalid if more than three items are not completed. We also had to rely on patient recollection of their functional baseline at the time of the fracture which may not be fully accurate. Due to time restraints, data on QOL or specific socioeconomic factors was not collected so associations with these could not be explored. Finally, we did not report on surgical techniques or radiographical outcomes though these have been investigated extensively in other studies.

6.4.5 Conclusions/Recommendations

We showed a significant correlation between dominant hand fracture, prolonged hospital admission, BMD, polypharmacy, recurrent falls, previous fracture and low body weight and poorer outcomes including pain and disability at up to one year after the fracture. Frailty, age, gender and co-morbidities were also shown to be associated with some outcome measures though the associations were not as consistent. The identification of subgroups at risk of poorer outcomes can help target rehabilitation and medical interventions to provide more meaningful interventions and ultimately improve the outcomes of patients following wrist fracture. Therefore, in planning care for patients following fractures, it is important to know factors predictive of future fracture. It is also useful to be aware of other factors that increase the likelihood of chronic pain and disability. This can could help plan clinical services aappropriate for individuals who may be at higher risk of complications. Having more information about our patients, patient outcomes and factors associated with these outcomes can also help us in our advocacy for more comprehensive assessment, targeted interventions, and tailored educational strategies. This work also highlights the value of observational research in exploring factors potentially contributing to poorer outcomes and the need for high quality cohort studies.

Chapter 7: Conclusion

This thesis includes the largest study in Ireland to characterize patients with DFF and the only one to prospectively follow up and assess outcomes over a one-year period post fracture. It is also the first study to ever explore the relationship between frailty (as measured by the CFS) and patients outcomes post DFF.

7.1 Patient characteristics and treatment gap

The results of this thesis highlight the high prevalence of osteoporosis (41.5-62.6%) in patients with wrist fracture, with only 10% in study 1 and 3 having normal BMD. We identified that of those with DFF, lower BMD was more likely in females, older and underweight adults . Other factors associated with a densitometric diagnosis of osteoporosis in my third study included frailty, low dietary calcium intake and reduced grip strength. Furthermore, between 23.9% (study one) and 45.9% (study three) had a history of a vertebral fracture(s) and one in six had a hip fracture. I also identified a relatively high prevalence of orthostatic hypotension in patients with DFF suggesting that its bedside assessment should be incorporated into falls risk assessment in FLS.

A significant proportion of patents with vertebral fracture(s) in study 2 had already sustained other fractures and had osteoporosis when assessed by DXA. These patients are at high risk of incident fragility fractures and need evaluation for potent treatments for osteoporosis, including teriparatide. Importantly, recognition of vertebral fractures provides an opportunity to intervene to reduce the risk of further fractures and their sequelae. However, a low proportion of the patients with VF were on anti-osteoporosis treatment (44.4%) as were those with DFF (12.8% in study 3 and 37.5% in study 1). In particular, males, younger patients and those with better T scores were less likely to be on therapy in the first study. These findings highlight the "treatment gap". This represents a gap between the number of people eligible for treatment for osteoporosis and receiving treatment. In Ireland Fracture Liaison Services are currently being developed to address this issue. Importantly, the majority of patients in study 3 who were prospectively followed were started on osteoporosis medications, had good therapy compliance and a low rate of incident fracture. This highlights the value of FLS and the benefit of multicomponent secondary prevention measures. My research also demonstrates a model of how patients with DFF can be captured and clinically followed up by a hospital based FLS.

7.2 Patient outcomes

Study 3 reported here in chapter 5 is, to our knowledge, the first to explore the characteristics of Irish adults requiring admission following wrist fractures for reasons other than surgery, as well as length of stay and estimated costs. Given that patients in the study requiring hospital admission at the time of fracture, were older, and more likely to be frail and take more medications, early geriatrician input at the time of acute presentation may be of benefit for this group as has been shown in patients with hip fracture. Given the findings that some of these patients moved to long term care or required home care packages to be in place prior to discharge, length of stay may be reduced with increased availability of these supports.

A recent research analysis identified a gap in the evidence regarding outcomes in older trauma patients. The findings in this study supports the value of using patient-reported measures as well assessing longer term health outcomes (178). I identified a significant improvement in PROMs in the first twelve months after fracture though there were high rates of chronic pain and disability at one year with 55/111 reporting ongoing pain and only 5.6% reporting no disability. Poorer outcomes including disability and pain at one year post DFF were correlated with dominant hand fracture, polypharmacy, recurrent falls, low body weight, prolonged hospital admission, lower BMD and previous fracture. Frailty, age, gender and co-morbidities were also shown to be associated with some outcome measures though the associations were not as consistent. The identification of subgroups at risk of poorer outcomes can help target specific interventions for patients such as multidisclipinary rehabilitation to improve outcomes post wrist fracture. This is also important in planning clinical services appropriate for those at higher risk for complications. Having more information about our patients, patient outcomes and factors associated with these, can also help in promoting advocacy for more comprehensive assessment, targeted interventions, and tailored educational strategies.

7.3 Improvements resulting from this research

This study identified the number and characteristics of patients presenting to St James's hospital with fragility fractures of the wrist. Prior to this research, only HIPE data was used for fracture identification, while now additional fractures are identified using NIMIS allowing the capture of all wrist fractures. This has resulted in a significant expansion of FLS within St James's hospital. We also reported valuable information that can help in future planning of FLS within the hospital.

We identified a high rate of non-attendance (36%). DFF are often considered to occur in younger fitter women whereas in our cohort a significant proportion of patients were frail and older - consideration should be given to this when planning appointment times, scheduling, location, duration and physical access to DXA The finding of good medication compliance highlights the importance of follow up in FLS and the potential benefit of shared decision making and discussion regarding anti-osteoporosis therapies at future appointments. During the study, relationships were

established with occupational therapy colleagues running the 'hand therapy group' and the interdisciplinary wrist fracture pathway was formalised.

7.4 Considerations for future research

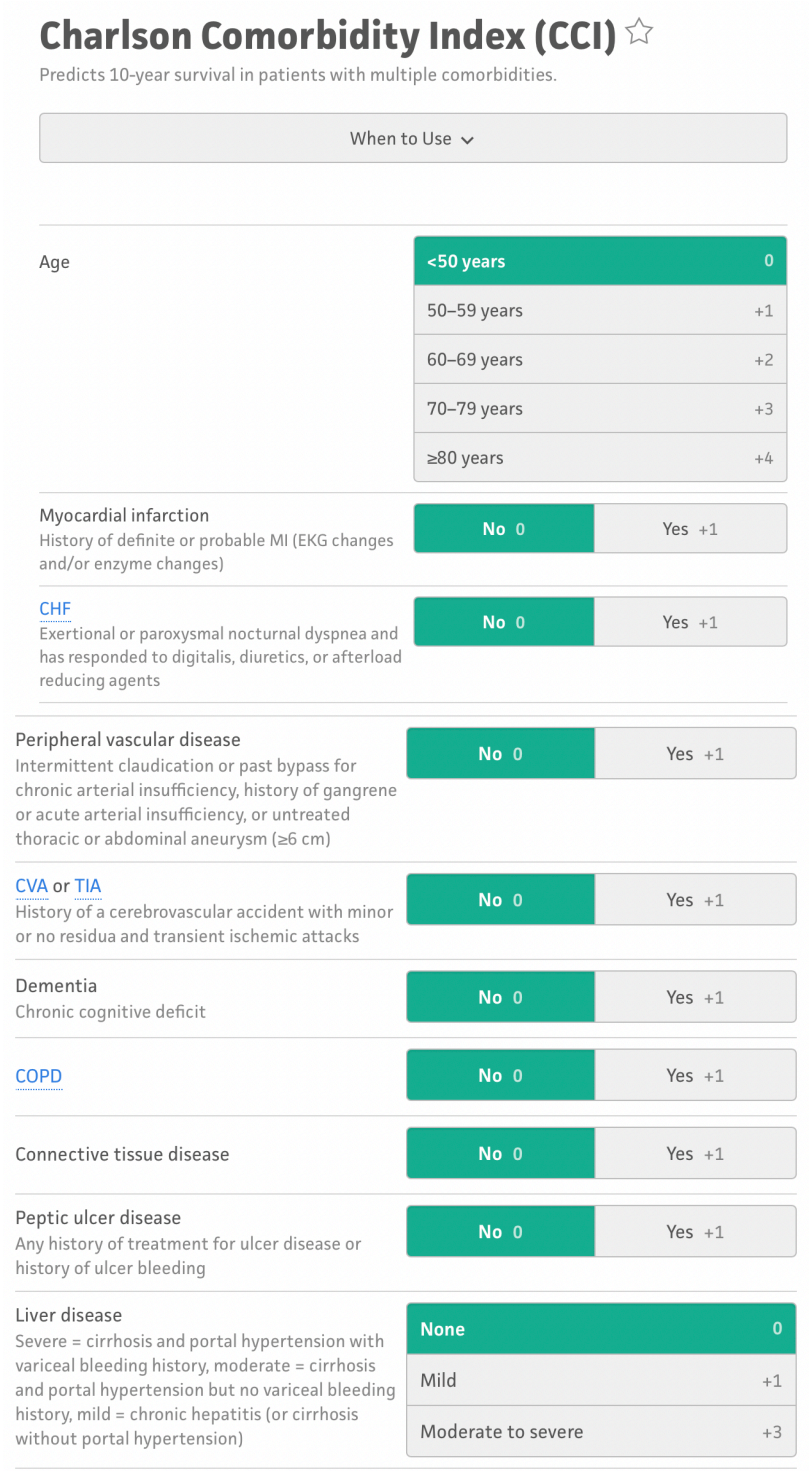
The first two studies examined patient data derived from a local database maintained in the Bone Health Service at St James's Hospital. However, as FLS is established in Ireland, development of the national FLS Database (initally at several partiicipating hospital sites) will provide more opportunity for ongoing research on characteristics and clinical outcomes in patients with DFF. It will also help in the continuous development of services to match demand and needs of the patients.

We reported a high rate of early menopause in patients with DFF, though our study relied on self report. Further research could be conducted to explore this relationship. A quarter of our cohort had a significant postural drop in blood pressure on bedside assessment, suggesting that assessment for orthostatic hypotension might be incorporated into falls assessment for patients with wrist fracture. Further studies examining the impact of identification of OH and subsequent interventions on the risk of incident fracture would be useful.

These studies highlight the value of observational research in exploring factors contributing to poorer outcomes in patients with DFF. More high quality cohort studies should focus on some of the factors I identified as being important such as age, gender, comorbidities, affected side, BMD, recurrent falls, previous fracture, and polypharmacy.. It would also be useful for studies to explore the potential benefits of optimising the above factors in improving clnical outcomes and potentially incident fracture rates. In particular, studies comprising multicomponent interventions to targeted groups at higher risk of complications would be informative.

Appendix A: Charlson Comorbidity Index (MD Calc)

Online version (251)



Charlson Comorbidity Index (CCI) ☆

Predicts 10-year survival in patients with multiple comorbidities.

When to Use

Age	<50 years	0
	50–59 years	+1
	60–69 years	+2
	70–79 years	+3
	≥80 years	+4
Myocardial infarction History of definite or probable MI (EKG changes and/or enzyme changes)	No	0
	Yes	+1
CHF Exertional or paroxysmal nocturnal dyspnea and has responded to digitalis, diuretics, or afterload reducing agents	No	0
	Yes	+1
Peripheral vascular disease Intermittent claudication or past bypass for chronic arterial insufficiency, history of gangrene or acute arterial insufficiency, or untreated thoracic or abdominal aneurysm (≥6 cm)	No	0
	Yes	+1
CVA or TIA History of a cerebrovascular accident with minor or no residua and transient ischemic attacks	No	0
	Yes	+1
Dementia Chronic cognitive deficit	No	0
	Yes	+1
COPD	No	0
	Yes	+1
Connective tissue disease	No	0
	Yes	+1
Peptic ulcer disease Any history of treatment for ulcer disease or history of ulcer bleeding	No	0
	Yes	+1
Liver disease Severe = cirrhosis and portal hypertension with variceal bleeding history, moderate = cirrhosis and portal hypertension but no variceal bleeding history, mild = chronic hepatitis (or cirrhosis without portal hypertension)	None	0
	Mild	+1
	Moderate to severe	+3

Diabetes mellitus	**None or diet-controlled** 0 Uncomplicated +1 End-organ damage +2
Hemiplegia	**No** 0 / Yes +2
Moderate to severe CKD Severe = on dialysis, status post kidney transplant, uremia, moderate = creatinine >3 mg/dL (0.27 mmol/L)	**No** 0 / Yes +2
Solid tumor	**None** 0 Localized +2 Metastatic +6
Leukemia	**No** 0 / Yes +2
Lymphoma	**No** 0 / Yes +2
AIDS	**No** 0 / Yes +6

Appendix B: ISCD indications for BMD testing

Available in ISCD 2019 Official Positions Adult (13)

Indications for Bone Mineral Density (BMD) Testing

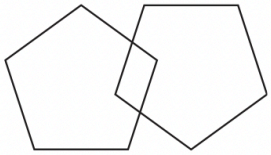
- Women aged 65 and older
- For post-menopausal women younger than age 65 a bone density test is indicated if they have a risk factor for low bone mass such as:
  - Low body weight
  - Prior fracture
  - High risk medication use
  - Disease or condition associated with bone loss
- Women during the menopausal transition with clinical risk factors for fracture, such as low body weight, prior fracture, or high-risk medication use
- Men aged 70 and older
- For men < 70 years of age a bone density test is indicated if they have a risk factor for low bone mass such as:
  - Low body weight
  - Prior fracture
  - High risk medication use
  - Disease or condition associated with bone loss
- Adults with a fragility fracture
- Adults with a disease or condition associated with low bone mass or bone loss
- Adults taking medications associated with low bone mass or bone loss
- Anyone being considered for pharmacologic therapy
- Anyone being treated, to monitor treatment effect
- Anyone not receiving therapy in whom evidence of bone loss would lead to treatment

Appendix C: Mini Mental State Examination

The Mini-Mental State Exam

Patient_____ Examiner _____ Date_____

Maximum	Score	
		Orientation
5	( )	What is the (year) (season) (date) (day) (month)?
5	( )	Where are we (state) (country) (town) (hospital) (floor)?
		Registration
3	( )	Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all 3. Count trials and record. Trials _____
		Attention and Calculation
5	( )	Serial 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.
		Recall
3	( )	Ask for the 3 objects repeated above. Give 1 point for each correct answer.
		Language
2	( )	Name a pencil and watch.
1	( )	Repeat the following "No ifs, ands, or buts"
3	( )	Follow a 3-stage command: "Take a paper in your hand, fold it in half, and put it on the floor."
1	( )	Read and obey the following: CLOSE YOUR EYES
1	( )	Write a sentence.
1	( )	Copy the design shown.



_____ Total Score

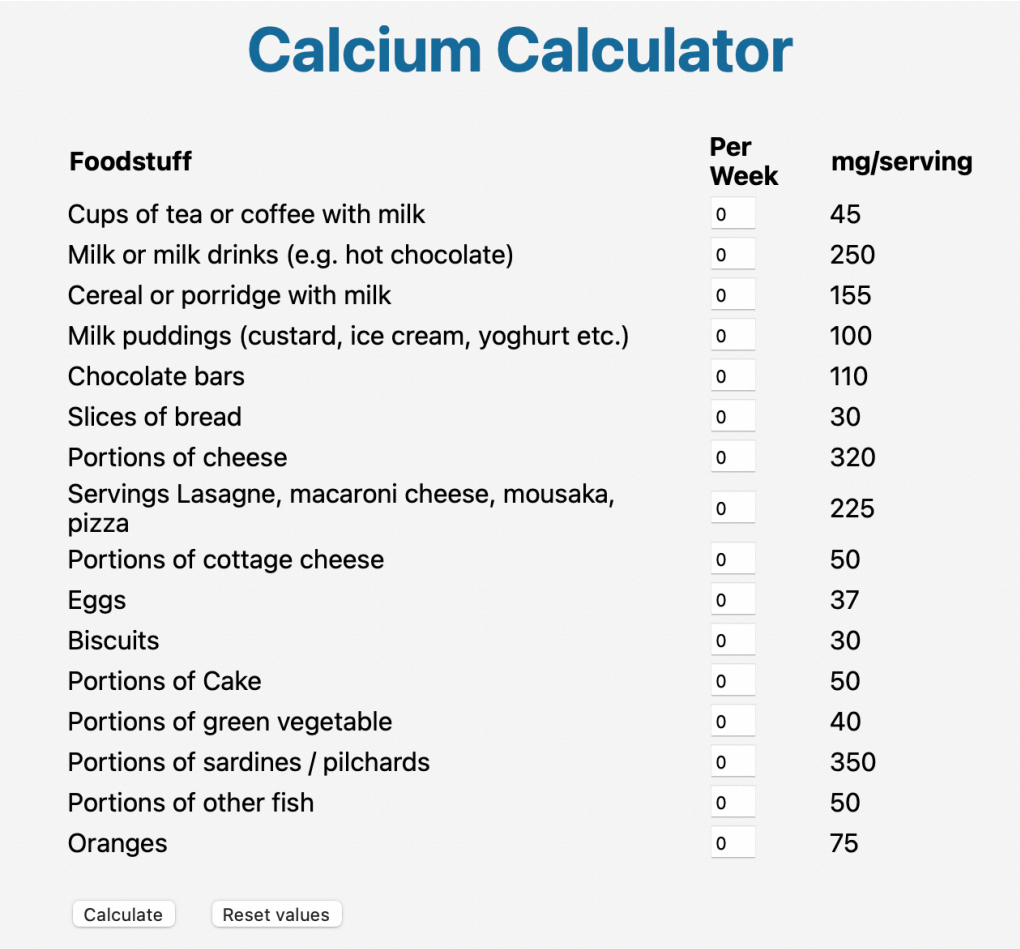
ASSESS level of consciousness along a continuum _____

Alert Drowsy Stupor Coma

"MINI-MENTAL STATE." A PRACTICAL METHOD FOR GRADING THE COGNITIVE STATE OF PATIENTS FOR THE CLINICIAN. *Journal of Psychiatric Research*, 12(3): 189-198, 1975. Used by permission.

Appendix D: CGEM Calcium Calculator

Available online (254)



Calcium Calculator

Foodstuff	Per Week	mg/serving
Cups of tea or coffee with milk	0	45
Milk or milk drinks (e.g. hot chocolate)	0	250
Cereal or porridge with milk	0	155
Milk puddings (custard, ice cream, yoghurt etc.)	0	100
Chocolate bars	0	110
Slices of bread	0	30
Portions of cheese	0	320
Servings Lasagne, macaroni cheese, mousaka, pizza	0	225
Portions of cottage cheese	0	50
Eggs	0	37
Biscuits	0	30
Portions of Cake	0	50
Portions of green vegetable	0	40
Portions of sardines / pilchards	0	350
Portions of other fish	0	50
Oranges	0	75

Calculate Reset values

Appendix E: Short Form 12

SF-12 Health Survey

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. **Answer each question by choosing just one answer**. If you are unsure how to answer a question, please give the best answer you can.

1. **In general, would you say your health is**:

☐1 Excellent ☐2 Very good ☐3 Good ☐4 Fair ☐5 Poor

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	YES, limited a lot	YES, limited a little	NO, not limited at all
2. **Moderate activities** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	☐1	☐2	☐3
3. Climbing **several** flights of stairs.	☐1	☐2	☐3

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	YES	NO
4. **Accomplished less** than you would like.	☐1	☐2
5. Were limited in the **kind** of work or other activities.	☐1	☐2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	YES	NO
6. **Accomplished less** than you would like.	☐1	☐2
7. Did work or activities **less carefully than usual**.	☐1	☐2

8. **During the past 4 weeks, how much did pain interfere with your normal work (including work outside the home and housework)?**

☐1 Not at all ☐2 A little bit ☐3 Moderately ☐4 Quite a bit ☐5 Extremely

These questions are about how you have been feeling during the past 4 weeks.
For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
9. Have you felt calm & peaceful?	☐1	☐2	☐3	☐4	☐5	☐6
10. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5	☐6
11. Have you felt down-hearted and blue?	☐1	☐2	☐3	☐4	☐5	☐6

12. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?**

☐1 All of the time ☐2 Most of the time ☐3 Some of the time ☐4 A little of the time ☐5 None of the time

Patient name: Date: PCS: MCS:

Visit type (circle one)
Preop 6 week 3 month 6 month 12 month 24 month Other:_____

Appendix F: Patient Rated Wrist Evaluation

Patient Rated Wrist Evaluation											
Rate the average amount of pain/difficulty you have had in your wrist over the past week by circling the number from 0 (no pain or difficulty) to 10 (the worst pain you have ever experienced or you could not do the task).											
PAIN:											
• At rest	0	1	2	3	4	5	6	7	8	9	10
• When doing a task with repeat wrist movement	0	1	2	3	4	5	6	7	8	9	10
• When lifting a heavy object	0	1	2	3	4	5	6	7	8	9	10
• When it is at its worst	0	1	2	3	4	5	6	7	8	9	10
• How often do you have pain?	0	1	2	3	4	5	6	7	8	9	10
FUNCTION--SPECIFIC ACTIVITIES:											
• Turn door knob using my affected hand	0	1	2	3	4	5	6	7	8	9	10
• Cut meat using a knife in my affected hand	0	1	2	3	4	5	6	7	8	9	10
• Fasten buttons on my shirt	0	1	2	3	4	5	6	7	8	9	10
• Use my affected hand to push up from a chair	0	1	2	3	4	5	6	7	8	9	10
• Carry a 10-lb object in my affected hand	0	1	2	3	4	5	6	7	8	9	10
• Use bathroom tissue with my affected hand	0	1	2	3	4	5	6	7	8	9	10
FUNCTION--USUAL ACTIVITIES:											
• Personal care activities (dressing, washing)	0	1	2	3	4	5	6	7	8	9	10
• Household work (cleaning)	0	1	2	3	4	5	6	7	8	9	10
• Work (your job or everyday work)	0	1	2	3	4	5	6	7	8	9	10
• Recreational activities	0	1	2	3	4	5	6	7	8	9	10
Score:											
Pain subscale:	**/50**										
Functional subscale (total divided by 2):	**/50**										
Total PRWE score:	**/100**										
Scoring: Each section can be summated individually or the total scores can be calculated & scored as percentages. For either method, the higher the score, the poorer the outcome.											

Source: Adapted from Lewis, C, Wilk, K, Wright, R. The Orthopedic Outcomes toolbox. Virginia: Learn Publications.

Appendix G: Disability of the Arm Shoulder and Hand

DISABILITIES OF THE ARM, SHOULDER AND HAND

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response.

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. Open a tight or new jar.	1	2	3	4	5
2. Write.	1	2	3	4	5
3. Turn a key.	1	2	3	4	5
4. Prepare a meal.	1	2	3	4	5
5. Push open a heavy door.	1	2	3	4	5
6. Place an object on a shelf above your head.	1	2	3	4	5
7. Do heavy household chores (e.g., wash walls, wash floors).	1	2	3	4	5
8. Garden or do yard work.	1	2	3	4	5
9. Make a bed.	1	2	3	4	5
10. Carry a shopping bag or briefcase.	1	2	3	4	5
11. Carry a heavy object (over 10 lbs).	1	2	3	4	5
12. Change a lightbulb overhead.	1	2	3	4	5
13. Wash or blow dry your hair.	1	2	3	4	5
14. Wash your back.	1	2	3	4	5
15. Put on a pullover sweater.	1	2	3	4	5
16. Use a knife to cut food.	1	2	3	4	5
17. Recreational activities which require little effort (e.g., cardplaying, knitting, etc.).	1	2	3	4	5
18. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	1	2	3	4	5
19. Recreational activities in which you move your arm freely (e.g., playing frisbee, badminton, etc.).	1	2	3	4	5
20. Manage transportation needs (getting from one place to another).	1	2	3	4	5
21. Sexual activities.	1	2	3	4	5

DISABILITIES OF THE ARM, SHOULDER AND HAND

	NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
22. During the past week, *to what extent* has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups? *(circle number)*	1	2	3	4	5

	NOT LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
23. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem? *(circle number)*	1	2	3	4	5

Please rate the severity of the following symptoms in the last week. *(circle number)*

	NONE	MILD	MODERATE	SEVERE	EXTREME
24. Arm, shoulder or hand pain.	1	2	3	4	5
25. Arm, shoulder or hand pain when you performed any specific activity.	1	2	3	4	5
26. Tingling (pins and needles) in your arm, shoulder or hand.	1	2	3	4	5
27. Weakness in your arm, shoulder or hand.	1	2	3	4	5
28. Stiffness in your arm, shoulder or hand.	1	2	3	4	5

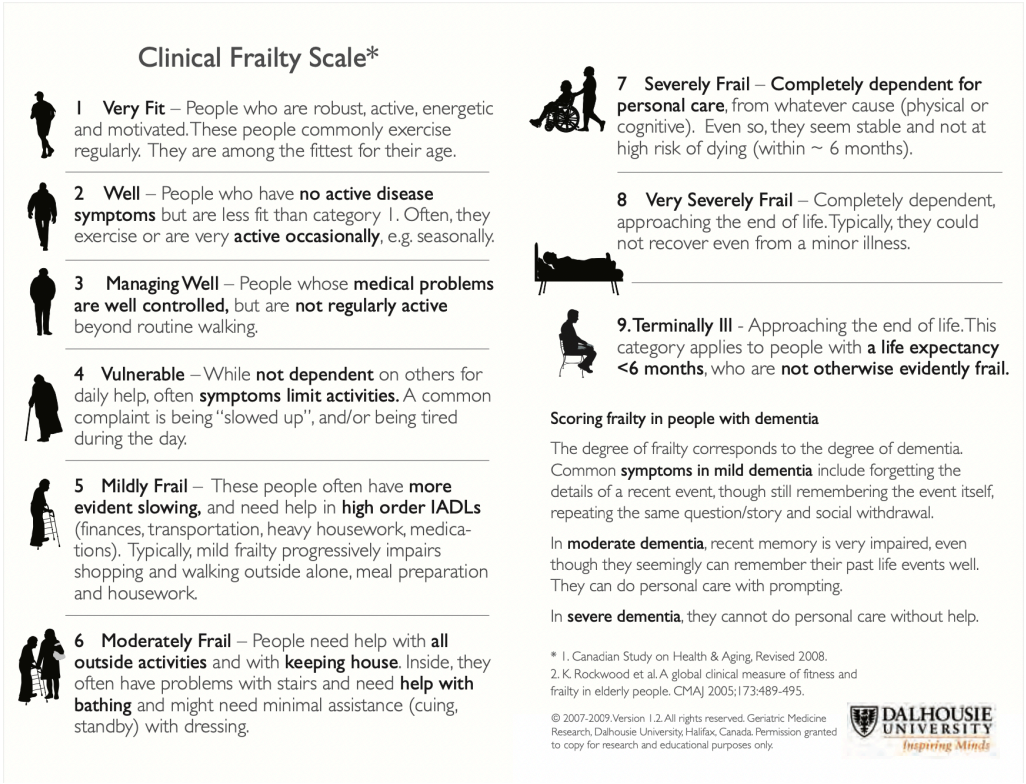
	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
29. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? *(circle number)*	1	2	3	4	5

	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
30. I feel less capable, less confident or less useful because of my arm, shoulder or hand problem. *(circle number)*	1	2	3	4	5

DASH DISABILITY/SYMPTOM SCORE = _____ ([(sum of n responses / n) - 1] x 25, where n is the number of completed responses.)

A DASH score may <u>not</u> be calculated if there are greater than 3 missing items.

Appendix H: Clinical Frailty Scale



Clinical Frailty Scale*

1 Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 Well – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 Managing Well – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 Vulnerable – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 Mildly Frail – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 Moderately Frail – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 Severely Frail – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 Very Severely Frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. Terminally Ill - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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