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Malnutrition, deficiency, and nutritional practice in patients with acute and chronic pancreatitis

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A thesis submitted towards the degree of

Doctor of Philosophy

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Submitted to the University of Dublin, Trinity College

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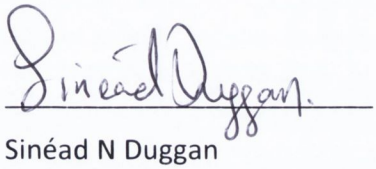

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Summary

Pancreatitis is an inflammatory disease of the pancreas and it may occur in either acute or chronic form, the former being life-threatening in its most severe form, and the latter being a progressive, irreversible disease with gradual destruction of the pancreatic parenchyma and deterioration of pancreatic function. Both disease subgroups have different needs regarding nutritional intervention, as well as diverse research requirements. Owing to sizeable gaps in the literature, guidelines on the management of nutritional deficiency, exocrine/endocrine function and bone health are lacking in chronic pancreatitis. For acute pancreatitis, the research-base is more extensive however adherence to best practice is questionable.

To address the dual themes of this thesis, there were 2 broad objectives:

- To investigate nutritional practice in acute pancreatitis
- To investigate malnutrition, deficiency and bone health in chronic pancreatitis

Seven studies were designed to fulfil these objectives, the first 3 of which compared nutritional practice in acute pancreatitis to the guidelines (on a local and international level; by retrospective audit and by electronic survey respectively). Analysis of local practice compared to the guidelines highlighted both discrepancies and strengths in nutritional management, including a favourable use of enteral over parenteral feeding and relatively low mortality rates. A delay in establishing enteral feeding was identified, although this was improved over the study period by the implementation of a bedside jejunal tube insertion technique. Assessment of international practice identified a continued reliance on parenteral feeding contradictory to the evidence base, as well as the identification of barriers to enteral feeding. In general, there was poor awareness of the guidelines, especially in smaller, non-university hospitals. Together, these studies showed that key aspects of practice in acute pancreatitis require improvement in order to comply with best-practice. These data will support the development of tailored interventions and educational strategies.

The latter 4 studies included a controlled cohort study which investigated malnutrition, vitamin deficiency and osteoporosis in chronic pancreatitis. This was followed by a meta-analysis of studies investigating the prevalence of osteoporosis. Finally, a second controlled cohort study of chronic pancreatitis patients examined bone metabolism and systemic inflammation. In summary, the data showed that vitamin deficiency in chronic pancreatitis was not uncommon, particular of vitamin D, although high serum levels of vitamins (hypervitaminosis) A and E also occurred. Poor muscle stores and poor strength were observed despite notable levels of obesity, indicating sarcopenic obesity. Other issues included under-treatment with pancreatic enzyme replacement therapy, poor glycaemic control among diabetics, frequent adverse symptoms, and for some, ongoing abuse of alcohol and heavy smoking. A high prevalence of osteoporosis and osteopenia were identified in the Irish cohort, as well as a high pooled prevalence from the meta-analysis of all published studies. There was elevated bone turnover in patients with chronic pancreatitis compared to controls, as well as higher systemic inflammation. Furthermore there were statistical associations between bone density, inflammation, smoking, and vitamin D. These findings will aid in the development of management frameworks, and will ultimately contribute to practice guidelines.

Together, these data will ultimately improve the management of patients with acute and chronic pancreatitis.

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List of abbreviations

1,25-OH D	1,25 hydroxyvitamin D
25-OH D	25, hyroxyvitamin D
AGA	American Gastroenterological Association
ANOVA	Analysis of variance
ANTICIPATE	Antioxidant Therapy for Painful Chronic Pancreatitis Therapy Evaluation
APACHE	Acute physiological and chronic health evaluation
ASPEN	American Society for Parenteral & Enteral Nutrition
ATP	Adenosine triphosphate
BAP	Bone alkaline phosphatase
BDA	British Dietetic Association
BMD	Bone mineral density
BMC	Bone mineral content
BMI	Body mass index
BMU	Bone metabolism unit
BTM	Bone turnover marker
c	Celsius
CCK	Cholecystokinin
X^2	Chi-squared statistic
CI	Confidence interval
CPr	Conference proceeding
CRP	C-reactive protein
CD	Crohn's disease
CT	Computed tomography
CTX	Carboxy-terminal telopeptide of type 1 collagen
CV	Coefficient of variation
DM	Diabetes mellitus
DXA	Dual-energy x-ray absorptiometry
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbant assay
EN	Enteral nutrition

ERCP	Endoscopic retrograde cholangio pancreatography
ESPEN	European Society for Clinical Nutrition & Metabolism
ESRI	Economic and Social Research Institute
FN	Femoral neck
FRAX	Fracture Risk Assessment
FSH	Follicular stimulating hormone
g	gram
GI	Gastro-intestinal
HbA1c	Haemoglobin A1c
HIPE	Hospital Inpatient Enquiry
IBD	Inflammatory bowel disease
ICU	Intensive care unit
IGF	Insulin-like growth factor
IL	Interleukin
INDI	Irish Nutrition & Dietetics Institute
IP	Internet protocol
IQR	Interquartile range
JA	Journal article
Kg	Kilogram
LH	Luteinising hormone
LOS	Length of stay
LV	Lumbar vertebrae
M	metre
MAFA	Mid-arm fat area
MAMC	Mid-arm muscle circumference
µg	Micrograms
MCP	Monocyte chemoattractant protein
M-CSF	Macrophage colony-stimulating factor
MCT	Medium-chain triglyceride
Min	Minute
MOOSE	Meta-analysis of Observational Studies in Epidemiology
MRI	Magnetic resonance imaging

MUAC	Mid upper-arm circumference
n	Sample size
NAPS	North American Pancreatitis Study
NG	Naso-gastric
NJ	Naso-jejunal
NOS	Newcastle-Ottawa scale
NPO	Nil per os
NS	Not significant
NTX	Urinary collagen type 1 cross-lined N-telopeptide
ONS	Oral nutritional supplement
OC	Osteocalcin
OHA	Oral hypoglycaemic agent
OPG	Osteoprotegerin
P1NP	Procollagen 1 aminoterminal propeptide
PEI	Pancreatic exocrine insufficiency
PERT	Pancreatic enzyme replacement therapy
PFA	Pain film of the abdomen
PICP	Procollagen 1 carboxyterminal propeptide
PIMS	Patient Information Management System
PN	Parenteral nutrition
PTH	Para-thyroid hormone
QOL	Quality of life
RANK	Receptor activator of NF-κB
RANKL	Receptor activator of NF-κB ligand
RCT	Randomised controlled trial
REE	Resting energy expenditure
RR	Relative risk
SAPE	Sentinel Acute Pancreatitis Event
SD	Standard deviation
SE	Standard error
SIRS	Systemic inflammatory response syndrome
SPSS	Statistical Package for Social Sciences

SVUH	Saint Vincent's University Hospital
TGF	Transforming growth factor
TNF	Tumour necrosis factor
TSF	Triceps skinfold
U	Units
UK	United Kingdom
UC	Ulcerative colitis
US	Ultrasound
USA	United States of America
WBC	White blood count
WHO	World Health Organisation

Dedication

This work is dedicated to my parents, Columba and Catherine Duggan, and to my husband and daughter, Paul and Cara Magill.

Chapter 1 Thesis introduction

1. 1 Introduction to thesis

Pancreatitis describes inflammation of the pancreas, and it may occur in either an acute or chronic form. Both acute pancreatitis and chronic pancreatitis have substantial implications for the nutritional competency of patients, requiring judicious nutritional assessment, treatment and monitoring. Yet research for many areas is scarce and where practice guidelines exist, adherence is uncertain. This thesis describes studies conducted on nutrition in both disease states. For acute pancreatitis, the studies examined clinical management in an acute setting, while for chronic pancreatitis, the studies investigated malnutrition and nutritional deficiency. Table 1 outlines the broad structure of this thesis. In Chapter 1, a background on the pancreas and pancreatitis is provided; Chapter 2 details the available literature on nutrition in acute and chronic pancreatitis; Chapter 3 describes the thesis outline, rationale and objectives; Chapter 4 describes the general methodology employed; Chapters 5, 6, 7 and 8 contain the studies which underpin this thesis. Each of these chapters contains an individual study introduction, as well as a discussion; finally, Chapter 9 provides an overall broad discussion of the work, focusing on the clinical implications and potential for future work.

Table 1.1 Thesis chapters in detail

Chapter	Title	Details
1	Introduction	General introduction and thesis outline Introduction to the pancreas Introduction to pancreatitis
2	Literature review	Nutrition in acute pancreatitis Nutrition in chronic pancreatitis
3	Thesis outline, rational and aims	
4	Methodology	Methodology common to the studies are detailed
5	Acute pancreatitis: Clinical studies	Study 1: Naso-jejunal tube insertion to facilitate EN in acute pancreatitis Study 2: An assessment of the nutritional and clinical management of patients with acute pancreatitis Study 3: A 6-country investigation of the nutritional management of patients with acute pancreatitis
6	Chronic pancreatitis: Malnutrition	Study 4: An investigation into malnutrition, nutrient deficiency, pancreatic function, pain and social issues in chronic pancreatitis
7	Chronic pancreatitis: Bone health	Study 5: The prevalence of osteoporosis and osteopenia in chronic pancreatitis Study 6: A systematic review and meta-analysis (prevalence of osteopathy in chronic pancreatitis)
8	Chronic pancreatitis: Bone metabolism	Study 7: Bone metabolism and systemic inflammation in chronic pancreatitis
9	Discussion	Summary of thesis findings, implications for practice, and future research

1.2 Introduction to the pancreas

The pancreas is a soft, lobulated, yellowish gland, extending nearly obliquely across the posterior stomach wall[1]. The wet organ weighs about 100g in adult males, 85g in females and 5g in the newborn. The adult gland is 14-18cm long, 2-9cm wide and 2-3 cm thick. It is divided into 4 regions: head, neck, body and tail[2]. It is located in the upper peritoneum, between the upper portion of the duodenum and the hilum of the spleen. The head fills the duodenum, and, near the Ampulla, is embedded within the duodenal wall (Figure 1.2 (a))[1]. The pancreas is both an exocrine and endocrine gland involved in the normal digestion and metabolism of fat, protein and carbohydrate. The main channel of drainage of pancreatic exocrine secretions begins in the tail by a confluence of smaller ducts. The pancreatic duct runs closer to the posterior surface through the body and neck into the head, receiving in its course the secondary ducts which join it in a regular fashion. In the head, the main duct inclines distinctly caudally and dorsally to its exit in the duodenum[2]. The pancreatic duct and bile duct penetrate the duodenal wall obliquely in parallel with each other. They may unite in the duodenal wall to form the hepatopancreatic ampulla (of Vater). The main pancreatic duct (of Wirsung) and the bile duct empty into the duodenal lumen at the major duodenal papilla of Vater, located 8-10cm distal to the pylorus[2].

The pancreas is characterised by its association with a plethora of vascular structures[2]. The coeliac and superior mesenteric arteries supply the pancreas with substrates for the synthesis of digestive enzymes and hormones. The venous drainage of the pancreas is primarily through the hepatic portal circulation. The pancreas has an extensive lymphatic drainage, although the lymphatics are not particularly prominent under physiological conditions. The potential for fluid and particulate drainage *via* the lymphatic drainage is evident when oedema, haemorrhage and cellular breakdown occur during pancreatitis[2]. The pancreas is supplied by branches from both the para-sympathetic and sympathetic divisions of the autonomic nervous system. Parasympathetic innervations provide part of the secretory stimuli for the pancreas and is supplied by the vagus nerve[2].

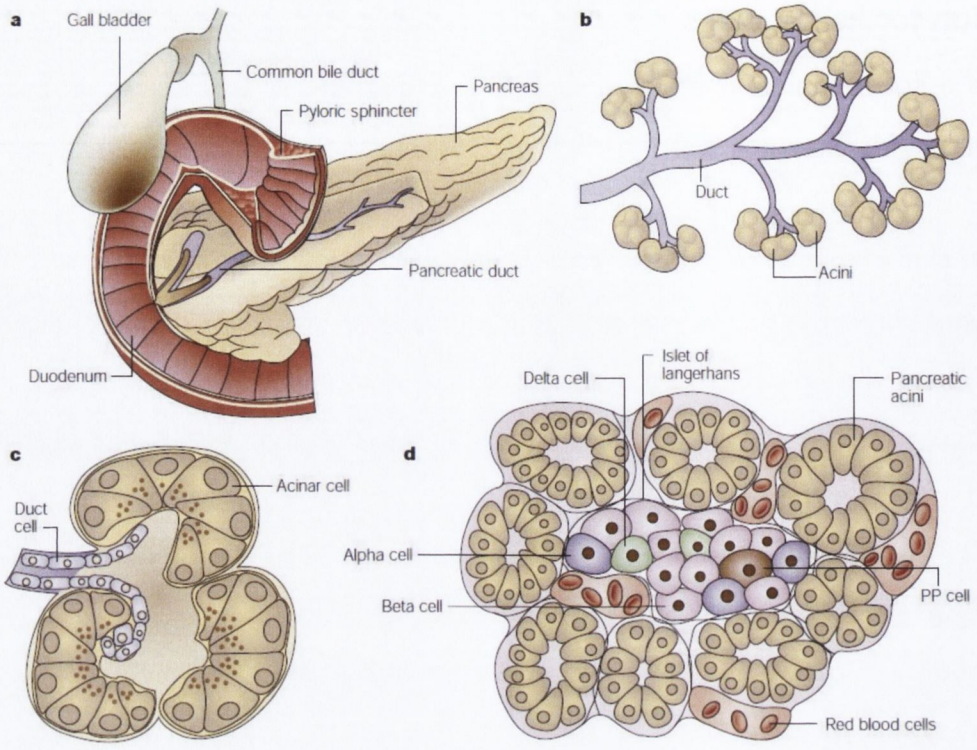

Figure 1.1 Anatomy of the pancreas

a: The gross anatomy of the pancreas
b: The exocrine pancreas
c: A single acinus
d: A pancreatic Islet cell embedded in exocrine tissue

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1.3 Exocrine function

0f 100g of human pancreas, 95-98% are composed of exocrine cells. The exocrine pancreas consists of three cell types; acinar cells, centroacinar cells and ductal cells, of which acinar cells are in the majority (Figures 1.1 (b) and 1.1 (c)). The acinar cells of the pancreas are typically zymogenic cells, consisting of a basally situated nucleus which is surrounded by basophilic cytoplasm, seen ultra-structurally as regular arrays of granular endoplasmic reticulum, interspersed mitochondria, and dense secretory granules[1]. The acinar cells are

connected to the pancreatic duct by ductules, lined by columnar epithelium, which secrete a bicarbonate-rich fluid.

1.3.1 Nutrient digestion

Optimal digestion and absorption of nutrients requires a complex interaction between motor and secretory function of the gastro-intestinal (GI) tract[4]. The digestion of macronutrients is a pre-requisite to absorption and occurs mostly *via* enzymatic hydrolysis. Pancreatic enzymes, in particular lipase, amylase, trypsin and chymotrypsin pay an important role. Enzymes of the brush border as well as other pancreatic and extrapancreatic enzymes, also participate in macronutrient digestion[4]

1.3.1.1 Normal exocrine function

The pancreas releases up to 2.5 litres of exocrine fluid per day. The digestive juices are stored in an inactive form inside zymogen granules within the pancreas, preventing autodigestion. To release the digestive enzymes, the zymogen granules fuse with the apical surface of the acinar cells, and are secreted into the ductular system of the pancreas. The ductules join together to form larger ducts, which empty into the duodenum at the Ampulla of Vater. The most important control of acinar enzyme and fluid secretion is exerted by the hormone cholecystokinin (CCK), and by the parasympathetic nerves with acetylcholine as the transmitter[1]. The presence of nutrients in the intestinal lumen is important in stimulating exocrine function; CCK is released in response to fatty acids and amino acids in the duodenum[5-6]. Secretin is stimulated by the presence of acid in the duodenum, and stimulates the secretion of a pancreatic juice high in bicarbonate concentration[5]. An alkaline environment is required in the duodenum for optimal enzyme activity, and the bicarbonate-rich fluid ensures that the acidic stomach juice is counteracted. The enzymes from the pancreas digest starch (amylase), fats (lipase) and protein (trypsin) and other proteolytic enzymes)[5]. Although amylase and lipase are secreted in an active form, the proteolytic enzymes are secreted as inactive substances that require activation.

1.3.1.2 Proteolytic enzymes

Trypsin is the key proteolytic enzyme which triggers the activity of all other pancreatic zymogens in a cascade manner[7]. It is secreted from the acinar cells as trypsinogens (there are 3 distinct forms providing 3 distinct forms of trypsin). Pancreatic juice entering the duodenum usually has no proteolytic activity. Enterokinase (a brush border enzyme of the duodenal mucosa which is active optimally at a pH of 6-9) converts trypsinogen to trypsin, in the process releasing trypsinogen activation peptide. Once trypsin has been liberated, it catalyses the activation of the other zymogens[7] (Figure 1.2).

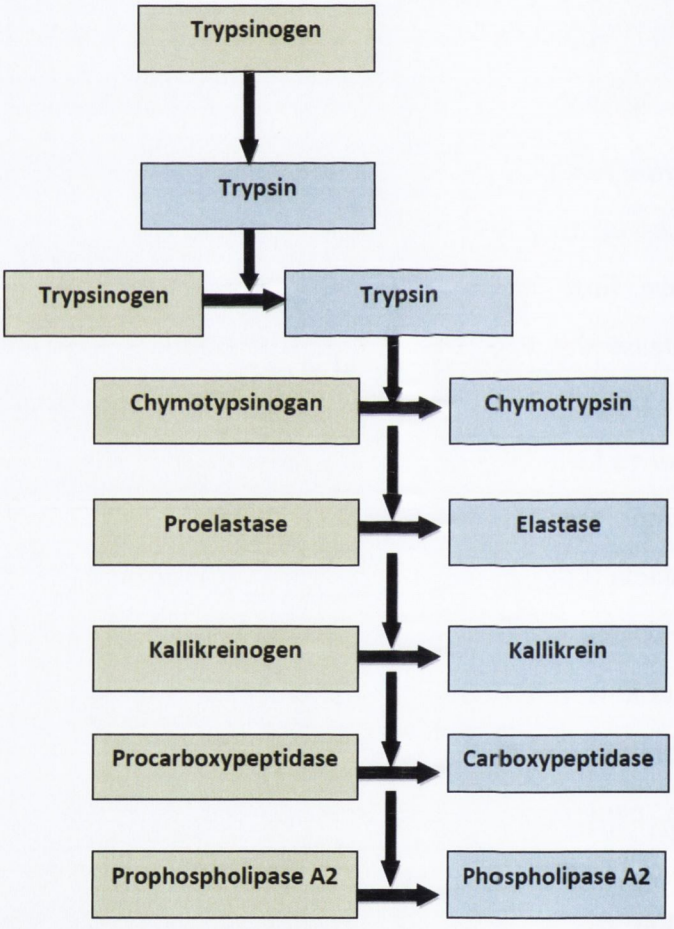

Figure 1.2 The trypsin cascade

Activation of trypsin by duodenal enterokinase leads to activation of other pancreatic zymogens (Adapted from Carter DC, Physiology of the Pancreas. In Trede & Carter (ed). Surgery of the Pancreas.)[7]

1.3.1.3 Lipolytic enzymes

Lipases are produced by both the stomach and intestines, but pancreatic lipase is of paramount importance in the digestion of fat[7]. Lipase rapidly hydrolyses the C1 and C3 bonds of triglyceride to produce free fatty acid and a monoglyceride. The enzyme is optimally active at an above-neutral pH, and is permanently deactivated at an acidic pH of <3.0[7].

1.3.1.4 Amylase

Alpha-amylase is present in saliva; but pancreatic amylase is the most important source of amylase production. Pancreatic amylase digests starch by breaking α1:4 glycoside links to liberate short chain polysaccharides, which are further digested by intestinal maltase and glucosidase.

1.3.1.5 Enzyme response to diet

Following a meal, enzyme delivery into the duodenum increases rapidly and reaches maximal levels within the first postprandial hour, or even within 20-30 minutes postprandially[4]. Following peak output, enzyme secretion decreases to a stable secretory rate, and decreases further after 3-4 hours to reach the interdigestive range at the end of the digestive period[4]. The degree and duration of the enzyme response are determined by caloric content, nutrient composition and physical properties of the meal. The route or site of nutrient administration also influences pancreatic enzyme response[4]:

- Oral ingestion and duodenal infusion of a complex nutrient formula cause similar increases in amylase, lipase and trypsin
- Jejunal nutrient infusion has 25% lower stimulatory potency than duodenal infusion
- Ileal nutrient perfusion inhibits enzyme secretion

In addition, the properties of the ingested meal may also influence the degree of pancreatic enzyme secretion (Table 1.2).

Table 1.2 Meal-specific factors that influence pancreatic response

Caloric content	**Maximal enzyme output occurs with intake of about 20 kcal/Kg** *For a 75kg person, this would be 1,500 kcal per day or 500 kcal per meal*
Nutrient composition	**Higher enzyme output with chronic ingestion of high fat diet *versus* high carbohydrate diet**
Physical properties	**A solid meal gives a more sustained enzyme response than an identical meal which has been homogenised** *Due to slower gastric emptying and an increased gastric and subsequently duodenal delivery of acid which may increase the pancreatic secretory response*

*Summary of Keller & Layer text (2000)[4]

1.3.1.6 Pancreatic secretory patterns

Pancreatic exocrine secretion occurs in 3 phases, each being coordinated with upper GI secretion and motility, and with entry of bile into the duodenum[7]. The *cephalic phase* which is mediated by the vagal cholinergic system and is triggered by sight smell and mastication of food, results in about half-maximal enzyme secretion rates[4]. The subsequent *gastric phase* accounts for a smaller part of the overall enzyme output and is probably mediated by gastropancreatic reflexes which are activated by gastric distention[4]. The quantitatively most important *intestinal phase* is induced by the entry of chime into the duodenum. Gastric acid, free fatty acids, essential amino acids and carbohydrates with the duodenum initiate the intestinal phase and maintain stimulation during the digestive period[4]. Late postprandially, pancreatic enzyme production declines to interdigestive levels. Ileal perfusion of lipids inhibits secretory and motor functions of the upper GI organs[4].

1.4 Normal endocrine function

The endocrine cells of the pancreas are arranged in nests or islets, which are spherical in outline and diffusely distributed in the parenchyma (Figure 1.1 (d)). The islet cells (known as the Islets of Langerhans) occupy about 1% of the volume of the pancreas, however they have a significantly higher concentration towards the tail of the pancreas[1]. At least four different islet cells exist, and are distinguished by their secretory granules[1]. The Islet cells are composed of 60% β-cells, which secrete the major anabolic hormone insulin. Insulin is necessary for the transmembrane transport of glucose and amino acids, glycogen formation in the liver and skeletal muscle cells, glucose conversion to triglycerides, and nucleic acid and protein synthesis[5]. The glucagon-producing α-cells make up 25% of the islets cells. Glucagon induces hyperglycaemia by its glycogenolytic activity in the liver. δ-cells secrete somatostatin, which suppresses both insulin and glucagon. PP cells secrete a unique pancreatic polypeptide which exerts a number of GI effects, such as the stimulation of the secretion of gastric and intestinal enzymes and the inhibition of intestinal motility[5]. The hormones are synthesised in the endoplasmic reticulum and are stored in the cytoplasmic granules from which they are released by the appropriate stimulus. The islet cells secrete hormones into the pancreatic vein, and then into the portal vein, where they join the splanchic circulation.

1.5 Acute pancreatitis

1.5.1 Introduction

Acute pancreatitis has been recognised as a critical illness for many years and it was first described by Reginald Fritz in 1889. As far back as 1925, Sir Berkley Moynihan wrote the following:

"Acute pancreatitis is the most terrible of all calamities that occur in connection with the abdominal viscera. The suddenness of its onset, the illimitable agony with which accompanies it and the mortality attendance upon it render it the most formidable of catastrophes."[8]

Acute pancreatitis was defined at the Atlanta Symposium in 1992 ('The Atlanta Classification') as an acute inflammatory process of the pancreas that frequently involves peri-pancreatic tissue and/or remote organ systems[9]. The Atlanta classification was further updated by international consensus in 2012[10]. The 2012 group defined acute pancreatitis as requiring two of the following three features:

1.) Abdominal pain consistent with acute pancreatitis (acute onset of persistent, severe, epigastric pain often radiating to the back)
2.) Serum lipase activity (or amylase activity) at least three times the upper limit of normal
3.) Characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CT), and less commonly magnetic resonance imaging (MRI) or trans-abdominal ultrasonography

1.5.2 Determination of severity

1.5.2.1 The Atlanta classification

The revised Atlanta criteria[10] classified the severity of disease into 3 groups. Mild acute pancreatitis was characterised by the absence of both organ failure and local/ systemic complications. Early discharge is likely and mortality is rare. Moderately severe pancreatitis is characterised by the presence of transient organ failure, or local/ systemic complications without persistence organ failure[10]. This classification of pancreatitis may resolve without intervention, or may require prolonged specialist care, but mortality is far less than that of severe acute pancreatitis. Severe acute pancreatitis is characterised by persistent organ failure, which may be single or multiple organ failure[10]. Mortality for those who develop persistent organ failure or systemic inflammatory response syndrome (SIRS) within the first few days of the disease are at increased risk of death (may be as great as 36-50%)[10]. The revisited classification stressed the importance of recognising that acute pancreatitis is an evolving, dynamic condition, and that the severity may change during the course of disease[10].

1.5.2.2 Other methods for assessing severity

Several pancreas specific clinical scores have been developed to identify patients at risk of developing severe acute pancreatitis at an early stage, so that clinical management may be optimised. These include the Imrie-Glasgow score, the acute physiology and chronic health evaluation (APACHE) II score, the multiple-organ dysfunction score and the pancreatitis outcome prediction score. Some of these have the disadvantage of only being determined after 48 hours, which is arguably well past the critical window. The APACHE II score has the advantage of being calculated upon presentation, however, specificity and sensitivity are reportedly low[11]. Other single serum markers that may guide assessment of severity include serum amylase and lipase, C-reactive protein (CRP), interleukins (IL) 1 and 6, procalcitonin, neutrophil elastase, and α1-antitrypsin[11]. In a comparison of several different prognostic systems and indices, Dambrauskas *et al* reported that the Glasgow-Imrie score is a valuable prognostic tool with sensitivity and specificity for predicting mortality of 70% and 83% respectively. The authors also stated that CRP remains the most useful among single biochemical markers[12]. All in all, early prediction is difficult and often inaccurate, and thus all patients should be initially managed as if the disease is severe. A CT at least 48-72 hours after diagnosis allows the determination of the CT-severity index, which has been shown to correlate with outcomes[11].

1.5.3 Presentation

Most patients have abdominal pain, usually continuous, but it may be colicky, centred in the epigastrum and right hypochondrium; in 50% of cases the pain radiated towards the back. Vomiting is frequent and diarrhoea, haematemis or malaena may occur[13]. Pain is usually obvious and severe, and there may be pyrexia. Clinically, patients may be shocked.

1.5.4 Aetiology

The two most common aetiological factors of acute pancreatitis are gallstone disease and alcohol abuse, together accounting for more than 80% of cases. However, the actual risk of developing acute pancreatitis with exposure to these risk factors is quite low; estimated at

2% for those with gallstones and 2-3% for those exposed to >60g alcohol per day for 20-30 years[14]. Nevertheless, the prevalence of pancreatitis is increased about four-fold among subjects with a history of alcoholism compared to those without.[15] Other causes of pancreatitis include metabolic abnormalities (such as hypertriglycerdiaemia), duct obstruction (related to a tumour or pancreas divisum), medications, and trauma. About 20% of cases are classed as idiopathic, where no identifiable cause can be found[16]. The American Gastroenterological Association (AGA) medical position statement on acute pancreatitis stated that it should be possible to identify the cause in at least 75% of patients[17], while the United Kingdom (UK) Working Party on Acute Pancreatitis in 2005[18] stated that less than 20% of cases should be classified as idiopathic. Aetiology varies with gender and age. Alcohol-induced pancreatitis is more common among men, and is highest in both sexes in the age group 35-44 years. Gallstone pancreatitis is more common among women, particularly over the age of 65. Both gallstone and idiopathic pancreatitis increase dramatically with age[19].

1.5.5 Incidence

The incidence of acute pancreatitis is rising, most likely due to an increase in alcoholic pancreatitis. The incidence of acute pancreatitis in Ireland is unknown. Research from our gorup demonstrated a 54% increase in admissions *via* accident and emergency with alcohol-associated pancreatitis over a 7 year period[20]. By examining data between 1997 and 2004, a particular increase in alcohol-related pancreatitis among females and among those age 20-30 years was highlighted. In the UK, there was a significant increase in acute pancreatitis admissions between 1963 and 1998, particularly among younger age groups[21]. The incidence of first attack of acute pancreatitis in England was reported at 10 per 100,000 population, lower than that of other European countries (The Netherlands, Germany and Norway; 16-20 per 100,000 population), and considerably lower than has been reported in other Scandinavian countries (Sweden and Finland) and in the United States (USA) (32-44 per 100,000 population).[14] The difference between geographical locations may be explained by differences in aetiologies. For example, in Scandinavian countries, a high alcohol intake may explain the high incidence in that region. The incidence of first attack of acute pancreatitis is increasing worldwide, as are the rates of hospitalisation for this disease. This will

undoubtedly impact on health care resources[14]. In 2003, the numbers of patients requiring hospitalisation for acute pancreatitis in the USA was 2.5 times greater than had been estimated[14].

1.5.6 Pathogenesis

The pathogenesis of acute pancreatitis relates to the inappropriate activation of tripsinogen to trypsin (which is usually not activated until it reaches the duodenum, see Section 1.5.1.2) coupled with a lack of prompt elimination of active trypsin within the pancreas[22]. Injury to the pancreatic acinar cells, by whatever cause, disrupts the physiological harmony between the lysosomes and zymogen granules that store potentially destructive enzymatic products[6]. This premature trypsin activation leads to autodigestion of the gland. Another important mechanism of injury is the obstruction of the pancreatic duct, leading to impaired bile flow with interstitial accumulation of fluid rich in pancreatic lipase, which can cause fat necrosis and local inflammation *via* stimulation of resident leukocytes and secretion of inflammatory cytokines. The resulting interstitial oedema impairs blood flow and causes ischaemic acinar cell injury[6]. The second stage of acute pancreatitis is amplification of the initial local pancreatic response affecting multiple organ systems[23]. IL-1 and IL-6, along with tumour necrosis factor-α (TNFα) are produced by neutrophils infiltrating the pancreatic parenchyma after induction of pancreatitis. This is followed by cytokine production, likely leading to adult respiratory distress syndrome and multisystem organ failure[23]. Although not causative for the disease, cytokines are involved in the progression of the disease beyond the pancreas. Organ dysfunction typically occurs 48 hours after disease presentation, and has provided a potential therapeutic window for anticytokinic therapy to prevent or modulate the onset of organ failure in severe disease[23].

1.5.7 Complications

Local complications include pancreatic necrosis (present in most patients with severe acute pancreatitis; may be infected or sterile), acute fluid collections (occur early in the course of acute pancreatitis; usually regress spontaneously, but may progress to become an abscess or

pseudocyst), pancreatic abscess (a circumscribed intra-abdominal collection of pus), and acute pseudocysts (a collection of pancreatic juice enclosed by a wall of granulation or fibrous tissue; formation requires 4 weeks from onset of acute pancreatitis). Systemic complications include shock, acute renal failure, respiratory failure and GI bleeding. Patients may have multiple complications concurrently or sequentially[24]. Approximately one-third to half of all deaths in acute pancreatitis occur in the first week, as a result of progressive multi-organ failure[25]. In patients with necrotising pancreatitis, the mortality is close to 17%, and may be as high as 30% in the case of infected necrosis[26].

1.6 Acute-recurrent pancreatitis

The term 'recurrent pancreatitis' is used to indicate recurrent attacks of acute pancreatitis in an otherwise (between attacks) normal pancreas[14]. Exocrine and endocrine insufficiency may be present in patients following recovery from a single episode of acute pancreatitis, even up to five years later[27]. This may be true even in the case of mild acute pancreatitis. Therefore it could be assumed that those suffering from *repeated* attacks of severe acute pancreatitis may have similar or greater functional deficiencies following apparent recovery. The sentinel acute pancreatitis event (SAPE) hypothesis was proposed in 2002 to explain the progression to chronic pancreatitis. The 'sentinel' event is an attack of acute pancreatitis which makes the gland particularly vulnerable in the recovery phase to additional insults (such as alcohol, metabolic and oxidative stress).[28] The SAPE theory is that in response to recurrent acinar cell injury activated macrophages start to release abundant amounts of transforming growth factor (TGF) β to suppress acute inflammation. These high levels of TGF-β ultimately result in pancreatic fibrosis, scarring and the loss of pancreatic function[29]. A study from five European countries demonstrated an acute pancreatitis recurrence rate of 27%, with alcohol being the most important aetiological factor for recurrent acute pancreatitis, followed by gallstones (25%).[14, 30]

1.7 Chronic pancreatitis

1.7.1 Definition

The Cambridge definition of chronic pancreatitis describes it as a chronic inflammatory disease of the pancreas characterized by irreversible morphological change and typically causing pain and/or permanent loss of function[31]. Chronic pancreatitis is characterized by the loss of pancreatic function due to the destruction of the acinar and Islet cells of the pancreas, and the development of fibrous scar tissue. Progressive loss of exocrine function results in maldigestion, weight loss, loss of muscle mass, reduced functional capacity, and micronutrient deficiency. Progressive loss of endocrine function leads to raised glucose levels and eventually diabetes (DM).

1.7.2 Pathology

The pathology of chronic pancreatitis is described as a progressive exocrine atrophy, with replacement of the normal pancreatic tissue with fibrous tissue leading to gland enlargement. The main duct becomes dilated, tortuous and strictured. Later the fibrous pancreas shrinks. Islands of exocrine parenchyma become surrounded by fibrous tissue. The ducts dilate and their inspissated secretions may calcify. The islet cells are initially preserved, but later their blood supply is compromised and atrophy occurs[32]. A review by Witt and colleagues in 2007 described research into the pathogenesis of chronic pancreatitis, which focused initially on large and small ducts, and then focused on the pancreatic parenchymal and non-parenchymal cells[33]. More recently, the genetics of chronic pancreatitis has been the focus of research. As the most common aetiology, the majority of studies relate to the pathogenesis of alcohol-induced chronic pancreatitis. Current opinion favours a concept known as the necrosis-fibrosis hypothesis (see Figure 1.3), which describes chronic pancreatitis as an initial acute process that progresses to chronic irreversible damage as a result of repeated acute attacks. Alcohol is thought to injure the pancreas by several hypothesised mechanisms[33]; by altering motility in large ducts resulting in reflux, by the precipitation of secreted pancreatic proteins within smaller ducts, by direct affect on the acinar cells causing autodigestion, by causing fragility of zymogen granules causing

premature enzyme activation, by alcohol-induced oxidative stress, by toxicity arising from alcohol metabolites, or by inducing disturbances in pancreatic micro-circulation. However, the pathogenesis of chronic pancreatitis is incompletely understood. In addition, as only a minority of heavy drinkers will develop acute pancreatitis, it is therefore thought that an additional insult or 'second hit' is required to precipitate a clinical attack of pancreatitis. Suggested precipitators are diet, amount and type of alcohol consumed, the pattern of alcohol consumption, hyperlipidaemia, and smoking. Genetic predisposition may also increase the sensitivity of the pancreas to injury.[15]

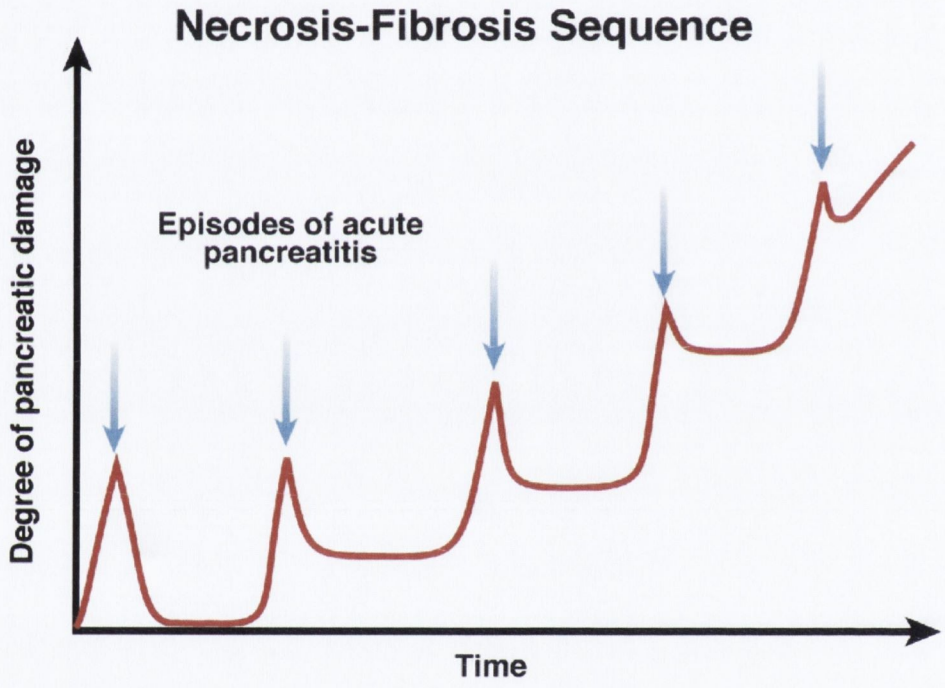

Figure 1.3 The 'necrosis-fibrosis concept' of progressive pancreatic injury

Cumulative pancreatic damage occurs with recurrent episodes of acute pancreatitis

Reprinted with permission[33]

1.7.3 Epidemiology

The overall prevalence of chronic pancreatitis in Europe is thought to be about 6-7 per 100,000 population[34], and the available data suggest increasing prevalence.[35] UK data from

the 1990's showed trends in increasing incidence based on national statistics for admissions.[36] An incidence of 7.9 per 100,000 per year was reported in 2001 in South and Central Moravia in the Czech Republic[37]. In 2002, a study in Northern Germany reported a crude incidence of 6.4 per 100,000 inhabitants from 1988 to 1995[14, 38]. Data from Japan (six national surveys have been conducted in Japan since 1970) have shown a definite increase in the prevalence of alcoholic chronic pancreatitis.[39] Throughout the world, chronic pancreatitis is more common in males, particularly alcoholic chronic pancreatitis; in both Europe and the USA, the ratio of male to female has been reported at 4 to 1. Chronic pancreatitis usually begins in adulthood; in a UK study, hospital admission for chronic pancreatitis peaked in the age groups between 35 and 54 years[36]. However, concrete serial data on the incidence and prevalence of chronic pancreatitis worldwide are actually surprisingly sparse.

1.7.4 Clinical presentation

The presenting symptom of most patients with chronic pancreatitis is abdominal pain, usually epigastric, dull and constant in nature. It is almost always localised in the upper half of the abdomen, from which it can radiate directly through to the back, or laterally around to the left or right flank. Initially the duration of pain is quite variable, ranging from several hours to several days, but as the disease progresses the attacks become more frequent and pain-free intervals shrink and vanish[40]. In some patients, chronic pancreatitis can be entirely silent, and presentation patients may present with the *sequelae* of exocrine or endocrine insufficiency: steatorrhoea, weight loss and DM. Less common initial presentations include biliary obstruction with recurrent episodes of mild jaundice, cholangitis, or vague attacks of indigestion[5]. Obstruction of the splenic vein by an inflamed tail of the pancreas can lead to left-sided portal hypertension, gastric varices and GI bleeding. Chronic pancreatitis and pancreatic cancer may present in a similar manner, making it difficult to distinguish between them[5].

1.7.5 Aetiology

1.7.5.1 Alcohol

The majority of cases in western countries have long been attributed to excess alcohol consumption. However, aetiology varies and constantly changes between countries and regions. Alcohol as an aetiology was reported to be as high as 95% of chronic pancreatitis in Australia[41]. In a 2008 review, Pezzilli and colleagues reported that alcohol as a main aetiological factor has been reported at a lower frequency than in the past[42]. In general, alcohol abuse is thought to account for up to 80% of all cases[14]. The degree of drinking appears to play a part; a key study in 2009 reported that there was a significantly increased risk of developing chronic pancreatitis, at an alcohol intake threshold at or above five drinks per day. However, not all alcoholics will develop chronic pancreatitis. The reason that some heavy alcohol drinkers develop liver cirrhosis and not pancreatitis is not clearly understood. In addition, patients may develop apparent alcohol-induced chronic pancreatitis on more arguably modest amounts of alcohol suggesting that other factors may play a contributory role. Little is known regarding individual variation in sensitivity to alcohol resulting in pancreatic damage. The reported increase in patient admissions with alcoholic acute pancreatitis, particularly among young people and among females, raises the concern that the incidence of chronic pancreatitis may also rise.[20]. A Japanese study showed that abstinence from alcohol (or occasional drinking only) reduced the risk of progression to chronic pancreatitis for those who have had one episode of alcohol-related acute pancreatitis, the risk being 14%. For those continuing to drink daily the risk was 23%, and for those drinking at the same levels as before the acute pancreatitis attack, the risk was 41%.[43] To date, there have been no studies on the prevalence, incidence or aetiology of chronic pancreatitis in an Irish population.

1.7.5.2 Tropical chronic pancreatitis

The form of idiopathic non-alcoholic chronic pancreatitis observed in malnourished patients in tropical and subtropical countries (including India and Africa), was traditionally termed tropical pancreatitis. This form of chronic pancreatitis tends to be characterised by an

advanced form of the disease, with large pancreatic calculi that affects very young malnourished individuals who often develop DM and have an aggressive course of the disease[44]. Traditionally, the intake of the root vegetable cassava (*Manihot Esculenta*) was implicated in the aetiology of this form of pancreatitis. Cassava contains cyanide-like compounds that are normally detoxified in the body by sulphur-mediated conversion to thiocanates. Malnutrition can result in a deficiency of sulphur-containing amino acids and antioxidants, which is believed to contribute to free radical production and pancreatic injury. However, more recently Midha and colleagues showed that malnutrition is an effect rather than a cause of the disease[45]. It is now thought that the (idiopathic) chronic pancreatitis seen in India has a strong genetic predisposition, and that cassava and malnutrition are not true aetiologies[44].

1.7.5.3 Idiopathic chronic pancreatitis

Idiopathic chronic pancreatitis is diagnosed by exclusion of other potential aetiologies[46] and is thought to comprise two clinically district entities[46]:

1.) Early-onset idiopathic chronic pancreatitis, with onset of the first symptoms during the first two or three decades of life. Patients have a prolonged course of substantial pain and develop morphological and functional pancreatic damage, although more slowly than patients with alcohol and/or smoking aetiologies.
2.) Late-onset chronic pancreatitis, with first presentation of symptoms after the fifth decade of life. Patients usually have a more mild or painless disease course.

About 20% of cases are considered to relate to idiopathic pancreatitis, while 'other causes' make up 10% of cases[14].

1.7.5.4 Other causes

Other causes of chronic pancreatitis include pancreatic duct obstruction, pancreas divisum, cystic fibrosis, hypercalcaemia, autoimmunity, gene mutations and hypertriglyceridaemia.

Pancreas divisum is a congenital malformation of the pancreatic duct system where the dorsal and ventral pancreatic ducts fail to fuse during the second month of development[6]. Pancreas divisum has been shown to be associated with chronic pancreatitis. Although pancreas divisum is a congenital problem, symptoms of obstruction and chronic pancreatitis do not occur until adult life. It is thought that pancreas divisum itself does not cause pancreatitis, but could act as a co-factor with other genetic causes. One study found that the prevalence of chronic pancreatitis in those with pancreas divisum was highest in those with variants of the cystic *fibrosis transmembrane receptor gene*, compared to those with pancreatitis of other causes.[15, 47] The numbers of idiopathic chronic pancreatitis will diminish with increasing identification of putative genetic and environmental causes[33].

1.7.6 The TIGAR-O aetiological risk classification system

The TIGAR-O classification system categorised aetiological risk factors associated with chronic pancreatitis[48], and is displayed in Table 1.3. This system categorises the major risk factors according to toxic-metabolic causes, idiopathic, genetic, autoimmune, recurrent severe acute pancreatitis-associated chronic pancreatitis, and obstructive chronic pancreatitis. The classification is roughly based on prevalence of each aetiology, and each class has implications for potential treatment.

1.7.7 The effect of smoking

Although not classed as an aetiology, smoking increases the risk of developing pancreatic dysfunction in late onset idiopathic chronic pancreatitis[49]. Other studies have suggested that smoking is an independent risk factor for chronic pancreatitis development in alcoholics, and is independent of the amount of alcohol ingested[50]. Cigarette smoke has been shown to have direct toxic effects on the pancreatic acinar cells[51] and to increase the risk of pancreatic calcifications[49]. Notably, smoking doubles the risk of pancreatic cancer[52].

1.7.8 Diagnosis and classification

A limited consensus exists on the best method of diagnosing, staging and classifying chronic pancreatitis[48]. The diagnosis of chronic pancreatitis, especially in the early stages, is difficult to establish. Although chronic pancreatitis diagnosis may be suspected following presentation with suggestive symptoms (typically weight loss, malnutrition, pain, and fat malabsorption) clinical presentation is usually insufficient to reach a firm diagnosis. The symptoms described above are generally vague and unspecific for chronic pancreatitis. For a diagnosis, clinicians need to rely on diagnostic tests, the most reliable of which is open to debate. Diagnostic tests can be divided in to two groups; those which test pancreatic structure, and those which test pancreatic function. Endoscopic and radiological tests fall into the first category. Tests of pancreatic function include direct hormonal stimulation tests, measurement of faecal elastase-1, serum trypsin, faecal fat and serum glucose. Regarding classification, pancreatologists have struggled to achieve a manageable classification system of chronic pancreatitis. In the last five decades, more than ten different and adjusted classifications systems of chronic pancreatitis have been proposed to provide a basis for diagnosis, treatment and research[14]. In 1984, the Marseille classification was produced at an international symposium[53] and was invaluable in defining and identifying various subtypes and clinical entities. However, it is not widely applicable to clinical practice[54]. Others have included the Cambridge classification and the Zurich International classifications. The Cambridge classification, although widely used, does not distinguish the different forms of chronic pancreatitis on the basis of aetiology, nor does it help to clinically distinguish patients or the functional abnormalities associated with those specific aetiologies. Thus, the Cambridge classification proves more useful as a staging system once the diagnosis of chronic pancreatitis is made, rather than a system for classifying aetiology[48]. More recently, Bagul and colleagues reported an evaluation of the Manchester classification system. This system identifies 3 stages of disease; mild, moderate and end-stage – each with essential criteria[54]. Although the Manchester classification system appears to be practical, simple and feasible, it is yet to be widely validated by others.

1.8 The pancreas in nutrition

Due to its exocrine and endocrine function, the pancreas has a significant role in normal nutrition homeostasis. For this reason, damage or injury to the pancreas has considerably negative nutritional implications. The nutritional concerns differ according to whether the insult to the pancreas is acute or chronic. Chapter 2 discusses both acute pancreatitis and chronic pancreatitis and their respective nutritional implications.

Table 1.3 Aetiological risk factors associated with chronic pancreatitis: TIGAR-O classification system (version 1.0)

Toxic-metabolic
Alcoholic
Tobacco smoking
Hypercalcaemia: *Hyperparathyroidism*
Hyperlipidaemia (rare and controversial)
Chronic renal failure
Medications: *Phenaectin abuse (possibly from chronic renal insufficiency)*
Toxins: *Organotin compounds (e.g. DBTC)*
Idiopathic
Early onset
Late onset
Tropical
Tropical calcific pancreatitis
Fibrocalculous pancreatic diabetes
Other
Genetic
Autosomal dominant
Cationic tripsinogen (Codon 29 and 122 mutations)
Autosomal recessive/ modifier genes
CFTR mutations
SPINK1 mutations
Cationic tripsinogen (Codon 16,22,23 mutations)
α_1- Antitrypsin deficiency (possible)
Autoimmune
Isolated autoimmune chronic pancreatitis
Syndromic autoimmune chronic pancreatitis
Sjörgen syndrome-associated chronic pancreatitis
Inflammatory bowel disease (IBD)-associated chronic pancreatitis
Primary biliary cirrhosis-associated chronic pancreatitis
Recurrent and severe acute pancreatitis
Post-necrotic (severe acute pancreatitis)
Recurrent acute pancreatitis
Vascular diseases/ ischaemic
Postirradiation
Obstructive
Pancreatic divisum
Sphincter of Oddi disorders (controversial)
Duct obstruction (e.g. tumour)
Preampullary duodenal wall cysts
Post-traumatic pancreatic duct scars

Chapter 2 Nutrition in acute and chronic pancreatitis: a review of the literature

2.1 Nutrition in acute pancreatitis

2.1.1 Enteral and parenteral nutrition – an introduction

In acute pancreatitis, as in many clinical conditions, normal oral diet may be impossible or contraindicated, necessitating artificial nutrition support. This may be done by two broad methods. Enteral nutrition (EN) refers to liquid nutrition provided *via* the GI tract using enteral feeding tubes. Feeding tubes may be inserted through the nasal passage (or less frequently the oral passage), into the stomach (naso-gastric, NG), duodenum (naso-duodenal) or jejunum (naso-jejunal, NJ). Where nasal tubes are unfeasible, or where tube feeding is required for a prolonged period, tubes may be inserted through the stomach or bowel wall (gastrostomy, jejunostomy). Parenteral nutrition (PN) refers to nutrition provided intravenously. PN is administered where the GI tract is compromised, injured, or inaccessible. PN may be administered *via* a peripheral vein, or *via* a central vein.

2.1.2 Requirement for nutrition

2.1.2.1 Mild acute pancreatitis

The nutritional management of acute pancreatitis varies according to its severity. In up to 75% of cases, the disease is in the mild form, with an uncomplicated disease process and a mortality rate of <1%[55]. Traditionally, in mild disease, the patient usually recommences oral diet within 3-7 days[55] following an initial period of *nil per os* (NPO). There is no evidence that artificial nutrition support improves outcomes in mild acute pancreatitis[55-56], and the disease has little impact on nutritional status or on energy and substrate metabolism[56]. Whether or not this is true in the presence of pre-existent malnutrition is not known. However, where oral diet is not possible for a prolonged period due to pain, EN should be considered[56].

2.1.2.2 Severe acute pancreatitis

In severe cases, mortality may be as high as 30%[17]. Severe acute pancreatitis may result in a SIRS and a consequent increase in metabolic demands. This systemic response may progress to multi-organ disease and metabolic alterations are frequent. The basal metabolic rate increases due to inflammatory stress and pain, leading to an increase in total energy expenditure[57]. Most patients are catabolic, with high energy expenditure and enhanced protein catabolism[58]. In a small study, Dickerson *et al* found that almost all septic acute pancreatitis patients were hypermetabolic, while only 61% of those without sepsis were hypermetabolic[58]. The presence of a severe negative nitrogen balance will negatively affect nutritional status and disease progression. In a trial by Sitzman *et al*, acute pancreatitis patients with a negative nitrogen balance had a tenfold higher mortality rate than those with a normal nitrogen balance[59]. There is a net loss of protein, with an increase of nitrogen loss in the urine of up to 20-40 gram (g) /day[55]. Gluconeogenesis increases, while the concurrent decrease in glucose oxidation results in glucose intolerance in acute pancreatitis frequently necessitating insulin administration. The effect of a poor baseline nutritional status on outcomes is unknown, although undernutition is a known risk factor for complications and morality in other diseases[56]. As alcohol is a major aetiological factor in acute pancreatitis, the frequent occurrence of undernutition in alcoholism should be considered. Meanwhile, obesity is known to be associated with a poor prognosis[56].

2.1.3 Controversies in feeding

Although nutrition has been generally accepted to benefit those with severe acute pancreatitis, the timing, method and type of feeding remains controversial. PN by its nature avoids the GI tract, and was traditionally provided to acute pancreatitis patients to prevent stimulation of the pancreas, termed 'pancreatic rest'. Intuitively, PN should be an ideal method of feeding; quick, easy to initiate, well-tolerated and without the complications associated with the use of feeding tubes. However, studies have increasingly shown that EN is superior to PN, and the optimal method of providing nutrition support in severe acute pancreatitis has been the subject of debate and several recent systematic reviews and meta-analyses.

2.1.4 EN and PN

2.1.4.1 Meta-analyses and systematic reviews: PN versus EN

In 2004, Marik and Zaloga conducted a meta-analysis comparing PN and EN in acute pancreatitis[60] and six studies were deemed suitable for inclusion. They found that EN was associated with a significantly lower incidence of infections, reduced surgical intervention and reduced hospital length of stay (LOS). No difference was seen in mortality, or in non-infectious complications. This meta-analysis was limited by the quality of studies therein; at least 4 were of questionable quality, and none were blinded. Low overall numbers (n = 263) led to wide confidence intervals (CI), and the authors commented that publication bias may have prevented the publication of negative or neutral studies. Nevertheless, following its publication, this meta-analysis formed the cornerstone for the use of EN in acute pancreatitis.

It was followed in 2006 by a further systematic review by McClave *et al* which examined 119 studies on nutrition in acute pancreatitis[61]. Of these, 27 prospective randomised controlled trials (RCTs) were considered eligible for inclusion. They similarly concluded that EN resulted in better patient outcomes than PN with regard to infectious complications, organ failure, hospital LOS, but again notably, not mortality. Addressing perhaps the most critical question of all, the authors could not find evidence that EN was better than 'no nutrition', except in the post-operative acute pancreatitis patient.

Petrov and colleagues published a further systematic review in 2008 which addressed the issue feeding *versus* 'no nutritional intervention'[62]. This review had three strands; comparing EN with no nutrition, PN with no nutrition, and EN with PN. Fifteen RCTs were included in this review. Regarding EN *versus* PN, 11 studies were reviewed, and use of EN was associated with a statistically significant 58% reduction in the risk of infectious complications, and a non-significant 40% reduction in death. Three studies compared PN with no nutrition. The use of PN was associated with a statistically non-significant increase of 36% in the risk of infectious complications, and a statistically significant reduction of 64% in the risk of death. Comparing EN to 'no nutrition', only one RCT was identified. Due to the small amount of data, an adjusted statistical method found that EN, compared with no nutrition, resulted in a statistically significant 78% reduction in the risk of death and a (non-significant) 44%

reduction in infectious complications. Although clearly limited by the number and quality of the individual studies, together these meta-analyses summarise the best available evidence and provide some substantiation to the view that EN has clinical benefits over PN for patients with severe acute pancreatitis.

2.1.4.2 The mechanism of a beneficial effect of EN over PN

The clinical benefits of EN may be due to the maintenance of gut barrier function by EN, and the theory that enteral amino acids may be more effective (than PN) in supporting splanchic protein synthesis. In fact, the GI tract is increasingly seen as a potential source for SIRS, with the possibility of clinical progression to sepsis, multi-organ failure, and death[55]. This seems to be most common in a metabolically deprived gut[55]. While the normal GI tract maintains microbial flora, prolonged disuse (with or without PN) results in bacterial overgrowth and a reduction in gut contractility, which may lead to an increase in virulent organisms to displace the commensal bacteria present in the tract[63-64]. Even short periods of disuse affect gut integrity and may cause gut permeability and the translocation of bacteria which may bind to the lymphoid tissue in the GI tract leading to the upregulation of systemic immunity[63]. A systemic inflammatory cascade results from the activation of macrophages and the proliferation of lymphocytes[63-64]. Starvation exacerbates the situation by causing a decreased proliferation of anti-inflammatory lymphocytes[63]. Therefore, the protection afforded to the gut during enteral feeding, and the deprivation of nutrients within the gut during parenteral feeding may account for some of the clinical benefits of EN over PN[64]. PN also confers several direct disadvantages over EN. Catheter-related infections may increase morbidity in PN, and insidious overfeeding (which is usually prevented during EN due to patient intolerance) is more likely in PN potentially leading to hazardous complications including hyperglycaemia and metabolic disturbances.

2.1.4.3 Supplementary PN

Despite the preponderance of studies recommending EN over PN, where EN is not tolerated PN is necessary to avoid rapid nutritional deterioration. The guidelines recommend that PN

should be administered where EN is not possible, and where caloric goal cannot be reached with EN alone[55].

2.1.4.4 NG or NJ feeding

While the use of EN over PN in severe acute pancreatitis has been accepted as best practice, it seems contradictory that feeding into the stomach could be tolerated in this group. Most early studies on EN in pancreatitis utilised post-pyloric feeding. Feeding into the jejunum, and particularly, beyond the Ligament of Treitz should allow enteral feeding, while preventing stimulation of the injured pancreas. In 2005, a UK study[65] challenged the accepted wisdom by comparing early NG feeding to early NJ feeding, and demonstrating no difference in mortality between the groups. In this study, 5 of the NG fed patients (n = 27; 18.5%) died, compared to 7 of the NJ fed patients (n=22; 31.8%). However, while the difference in mortality between the groups was not statistically different, the overall mortality was notably high. It is possible that the tip of the tube was in the duodenum rather than in the jejunum, as the tube type and placement technique used could not have achieved true jejunal placement. Therefore, both groups may have been equally pro-inflammatory. Since that study, others have sought to examine NG feeding as a method of feeding in acute pancreatitis.

A study by Eckerwall and colleagues in 2006 compared the efficacy and safety of early NG feeding with PN in severe acute pancreatitis[66]. Fifty patients were included in the study. They found that hyperglycaemia was higher in the PN group, while total complications and pulmonary complications were higher in the NG group. They found no beneficial effects on intestinal permeability or the inflammatory response by the NG treatment. However, with a total sample size of 50, it is probable that this study was not sufficiently powered to detect differences between the groups if they existed. In addition, the usefulness of comparing NG to PN is questionable. Comparing NG to NJ should be the most pertinent question.

A study published in 2006 by Kumar *et al* compared NG to NJ feeding in severe acute pancreatitis (n = 31)[67]. This study could be similarly criticised for comparing NG feeding to duodenal feeding (rather than jejunal feeding) and in fact, the data showed no difference between the groups regarding mortality, requirement for surgery, pain or feeding

intolerance. There was also a notable delay in commencing EN in both groups (7.8+6.5 and 5.7+4.7 days after onset of symptoms respectively). Small numbers also rendered this study insufficiently powered and therefore the reliability of the conclusions should be questioned. A meta-analysis published in 2008 included the 3 studies discussed above, along with an early cohort study from the UK group[68]. The total subjects included amounted to only 92. Although the meta-analysis concluded that NG feeding appears safe and well-tolerated in severe acute pancreatitis, the results must be viewed with caution due to the questionable quality of the studies and low patients numbers. An adequately-powered RCT on NG *versus* NJ feeding in severe acute pancreatitis is required prior to the routine adoption of NG feeding in this challenging group.

2.1.4.5 NJ tube insertion

From a practical viewpoint, the use of NG feeding is attractive. It potentially saves time, is cheaper, easier, and it relies less on specialist personnel and equipment. To date, NJ feeding has relied on endoscopic or radiological tube placement with the associated resource and cost implications. The blind placement of NJ tubes by bedside is a feasible alternative to these more costly and complex methods. Chapter 5 details a study on the bedside insertion of NJ tubes[69].

2.1.5 Optimal feeding formula

Since EN is now considered best practice in the management of severe acute pancreatitis, attention has since focused on which type of enteral formula would be most beneficial. EN formulae can be broadly stratified into 3 categories; polymeric (whole protein) feeds, (semi)elemental feeds, and immuno-enriched feeds. Theoretically, elemental or semi-elemental feeds should confer benefits due to their 'pre-digested' nature; requiring minimal intestinal absorption and pancreatic stimulation. Immuno-enriched formulae may be enhanced with putative immune system modulating substrates such as glutamine, arginine, and omega-3 poly-unsaturated fatty acids. A systematic review published in 2009 compared the tolerance and safety of various enteral formulations in patients with acute pancreatitis[70].

Twenty RCTs were included in the final analyses, only one of which was multicentred. Twelve of the 20 trials included patients with severe acute pancreatitis only, while the remainder included both mild and severe acute pancreatitis. In all acute pancreatitis patients, the use of semi(elemental) formulae did not result in a significant difference in the risk of infectious complications or death. The authors found that fibre-enriched (polymeric) formulae could be safely administered in acute pancreatitis, and that supplementation with immuno-nutrients or probiotics did not improve clinically meaningful outcomes. This suggests that the more expensive elemental or semi-elemental feeds are not indicated in acute pancreatitis. The meta-analysis was limited by the quality of the included studies and the heterogeneous nature of the feed types, methods of feeding, fibre-type and patient types. That the acute pancreatitis patient might tolerate polymeric feeds seems contradictory to the 'pancreatic rest' theory. However, as NJ feeding was employed in the majority of studies included, it is possible that the pancreas was not stimulated as feeding into the jejunum prevents pancreatic stimulation[71-72]. Whether or not the use of polymeric feeds results in favourable outcomes during gastric feeding in acute pancreatitis remains unclear. Future research should focus on the optimal EN formula in this group.

2.1.6 Timing of feeding

International management guidelines have recommended starting nutrition early in severe disease, (where there are complications) or where surgery is indicated to prevent the effects of nutrient deprivation[55]. However, there is no absolute qualification of what constitutes 'early feeding'. Studies in other critically ill populations indicate that there may however be an early window of opportunity following presentation with acute pancreatitis during which EN may positively alter the clinical course of disease. In one study on critically ill patients, feeding within 36 hours of presentation reduced infection by 55% and shortened LOS by 2.2 days.[73-75] Furthermore, it appears that in the critically ill, the deficits that builds during periods of prolonged fasting (termed 'cumulative caloric deficit') corresponds to increased duration of mechanical ventilation, longer hospital LOS, increased infections, and higher complication rates. Whether or not the same effect is present in acute pancreatitis is not certain, however, there is some evidence that establishing early EN in acute pancreatitis may

lead to better tolerance of feeding. Nevertheless, the putative benefits of *early* feeding in severe acute pancreatitis remain unproven by prospective trials. A systematic review by Petrov *et al* published in 2009 aimed to define whether the time of commencement of nutrition had an influence on the risk of clinically meaningful outcomes, including multi-organ failure, pancreatic infection, and mortality[76]. The dual objectives of the study (to compare types and timing of nutrition) provided results that were quite difficult to interpret. This may have been due to the fact that no studies have specifically investigated the effects of timing of feeding. Eleven RCTs were included in the analyses (n=451, range 17 to 89). The first objective was to compare EN *versus* PN among patients with mild or severe disease. EN commenced within 48 hours of admission was associated with significantly less risk than PN, in terms of multi-organ failure (relative risk (RR) 0.44, 95% CI 0.23 to 0.84; three RCTs), pancreatic infection (RR 0.46, 95% confidence interval (CI) 0.27 to 0.77; five RCTs), or mortality (RR 0.46, 95% CI 0.20 to 0.99; five RCTs). Findings were similar when nutrition was initiated within 24 hours of admission, as was the case in four RCTs. There was no statistically significant difference between the groups when nutrition was initiated more than 48 hours after admission. The second objective was to investigate early *versus* delayed nutrition among patients with mild or severe disease. There was no statistically significant interaction between early *versus* delayed groups for any outcome with feeding either 24 or 48 hours post admission. There was a trend for greater risk reduction associated with delayed nutrition for the outcome of pancreatic infectious complications, but not for other outcomes. In summary, the data suggested there is a risk reduction with EN over PN (regarding multi-organ failure, pancreatic infectious complications and mortality), but only if feeding is commenced within 48 hours of presentation. This systematic review was severely limited by the poor quality of some of the studies (five of eleven were considered low quality). It was also inherently limited by the fact that none of the studies actually sought to investigate the effect of timing, and thus the data could be described as indirect. An RCT directly comparing early feeding *versus* late feeding is required.

2.1.7 Guidelines for feeding in acute pancreatitis

Testament to the controversial nature of nutritional therapy in acute pancreatitis, a plethora of guidelines have been published in recent years aiming to provide direction for clinical practice. In 2002, the American Society for Parenteral and Enteral Nutrition (ASPEN)[77] published guidelines on nutrition in acute pancreatitis as part of their disease-specific guidelines, which were updated in 2009[78]. The European Society for Clinical Nutrition and Metabolism (ESPEN) published a series of guidelines; the "ESPEN Guidelines on Nutrition in Acute Pancreatitis" published in 2002[55], the "ESPEN Guidelines on Enteral Nutrition: Pancreas" published in 2006[56], and the "ESPEN Guidelines on Parenteral Nutrition: Pancreas" published in 2009[79]. In practice guidelines published by members of the practice parameters Committee of the American College of Gastroenterology[80], medical and surgical issues are discussed in detail. Therein, a section on nutritional support discusses the optimal delivery of nutrition in acute pancreatitis. Similarly, the AGA[17], and the UK Working Party on Acute Pancreatititis[18] consider nutritional guidelines as part of the overall management of acute pancreatitis. The guidelines are summarised in Table 2.1. Despite the quantity of guidelines published over the last ten years, there has been little research investigating adherence to guidelines. Chapter 5 details a study investigating dietetic practice to guidelines in acute pancreatitis.

Table 2.1 Summary of guidelines for the nutritional management of acute pancreatitis

	Mild acute pancreatitis	Severe acute pancreatitis	PN	EN route	EN formula	Surgery	Additions
ESPEN guidelines: Pancreatitis 2002[55]	-No evidence for EN / PN -If malnourished, nutrition role unclear -If oral diet delayed reconsider nutrition support	-Feeding essential -Early feeding recommended	-PN if EN insufficient -Contraindicated if Trigs >12 mmol/L	Jejunal route	Elemental or immuno-enriched feed		
ESPEN guidelines EN 2006[56]	-Nutrition support not indicated -Oral feeding when possible -If no oral diet for >5 days, EN indicated	-EN if possible -Early EN -Continuous EN if possible	Supplement EN with PN if needed	If gastric not tolerated, try jejunal	-Peptide-based safe -Standard should be tried if tolerated	Jejunostomy intra-operatively for post-operative feeding	
ESPEN guidelines PN 2009[79]		EN first choice	-Only if intolerant of EN -As EN increases, PN should be decreased -If Trigs >12 mmol/L, stop PN -PN contraindicated in Trig-associated pancreatitis				-Glutamine: >0.2g/Kg/day -Daily dose of micronutrients should be administered -No evidence for megadoses
AGA guidelines 2007[17]	No role for nutrition support if oral diet <7 days	EN (NJ) preferred *vs.* PN	May be required, e.g. in severe ileus	NJ preferred (*versus* PN)			
UK guidelines 2005[18]	No benefit for nutrition support No dietary restrictions	No evidence for nutrition support in all patients; EN if needed					
ASPEN guidelines 2009[78]	Nutrition support not required unless complications or no oral diet >7days	Insert EN tube when fluid resuscitation complete	If EN not feasible delay PN for 5 days	-NG or NJ -Tube lower in gut may be better tolerated	Specialised feed may be better tolerated		

2.2 Nutrition in chronic pancreatitis

Chronic pancreatitis results in progressive exocrine and endocrine dysfunction thereby affecting normal digestion and absorption of nutrients. The pancreas' exocrine and endocrine functions make it a key organ in nutrient digestion; the normally functioning pancreas may release up to 2.5 liters of exocrine secretions per day. Nutritional deficiency is not uncommon in chronic pancreatitis, driven by poor dietary intake, malabsorption, DM and alcoholism, however these concerns are frequently overlooked, potentially resulting in poor bone health, eye disorders and debilitating symptoms such as fatigue. Acute pancreatitis is the focus of most of the research, due to its immediate life-threatening nature, and there is a distinct gap in the literature in the case of chronic pancreatitis. Published nutritional guidelines have dealt mostly with acute pancreatitis[56]; the data is lacking in nutrition in chronic pancreatitis, as much of the evidence is low level. The aims of Section 2.2 are to describe the nutritional deficits that occur in chronic pancreatitis and to discuss the nutritional management. Chapters 6, 7 and 8 detail investigations into nutritional status and deficiency in chronic pancreatitis.

2.2.1 Drivers of malnutrition in chronic pancreatitis

2.2.1.1 Exocrine insufficiency

Loss of acinar cell function in chronic pancreatitis results in the reduced production and secretion of digestive enzymes. This causes maldigestion and malabsorption of both macronutrients (fat, carbohydrate, protein) and micronutrients. In particular, malabsorption of fat is problematic, causing fat excretion in the faeces. This symptom normally develops when pancreatic lipase secretion becomes less than 10% of normal[81]. Excretion of more than 15 grams of fat per day is considered severe[82] and the degree of exocrine dysfunction tends to be correlated with severity of disease[83].

Patients with chronic pancreatitis may exhibit a broad range of exocrine function[4]:

- Normal output

- 'Compensated': pancreatic exocrine insufficiency (PEI) where enzyme output less than normal but sufficient to prevent nutrient malabsorption
- 'Decompensated': severe PEI with clinical steatorrhoea

Several decades ago, DiMagno *et al* investigated pancreatic exocrine output in response to a mixed meal in patients with chronic pancreatitis exhibiting symptoms of severe PEI. They reported that digestive lipase output was in the region of 2.5 units (U)/min, which is less than 0.02% of normal (3,000 U/min)[84]. Layer and colleagues conducted similar studies in the 1990's and observed that severe PEI was associated with considerable maldigestion and malabsorption. Notably, in patients with chronic pancreatitis, about 40% of nutrients passed undigested into the ileum, compared to about 5% of nutrients in healthy adults. The passage of undigested nutrients into the ileum affects gastric secretion, gastric emptying, pancreatic exocrine function and intestinal transit[83].

Fat malabsorption in chronic pancreatitis is driven by many different factors. Insufficient secretion of pancreatic lipase, destruction of lipase due to acid, insufficient micelle formation due to inadequate bicarbonate production, or the precipitation of bile acids due to an acidic upper small intestine have all been implicated[4, 83]. Additionally, abnormally slow or rapid gastric emptying may affect nutrient absorption. A reduction in CCK production may impair gallbladder contraction compromising fat absorption. Lipase degradation within the small intestine lumen occurs more rapidly than that of the other enzymes, due to its greater instability against proteolysis[4]. Furthermore, although gastric lipase may compensate in small amounts for the destruction or deficiency of pancreatic lipase, the upregulation of gastric lipase secretion is incapable of compensating to any clinically relevant degree[4]. In contrast, the digestion of undigested protein and carbohydrate may continue in the small intestine due to the presence of intestinal brush border proteases and oligosacharidases[4]. Further carbohydrate metabolism may occur by fermentation by colonic microflora[85].

2.2.1.2 Assessment of exocrine function

The clinical inspection of stools to diagnose steatorrhoea is unreliable, except in the case of gross fat malabsorption[82]. In chronic pancreatitis, stools tend to be bulky and formed as

opposed to watery. Visible oil is virtually pathognomonic of chronic pancreatitis, representing fat malabsorption of 30-40g per day.[82] For the evaluation of exocrine pancreatic function, there are both direct and indirect tests.[86] The secretin-pancreozymin test may be considered the gold-standard test, but is time consuming, invasive and expensive, and unlikely to be available outside of specialised gastroenterology centres.[86] Indirect tests exist to measure the degree of fat malabsorption with varying effectiveness and practicality. The most accurate method of assessing fat maldigestion is a 72-hour faecal fat study, followed by the consumption of a diet with a precisely known fat content during the 72-hour collection period.[81] However this is impractical, costly and painstaking, and therefore substitute tests for fat malabsorption are required[82]. Pancreatic elastase-1 (faecal elastase-1) is a human specific enzyme that is not degraded during intestinal transit, and is enriched 5-6 fold in the faeces.[86] and therefore faecal elastase-1 is a very adequate test of pancreatic exocrine function[87]. Other benefits include the fact that the ingestion of oral enzyme preparation do not interfere with the test, and therefore pancreatic enzyme replacement therapy (PERT) does not need to be interrupted for the purposes of testing pancreatic function. Although the test is not sensitive enough to detect mild insufficiency, it is highly sensitive for the determination of moderate-to-severe disease[87]. Importantly, the patient does not need to ingest a specific substrate (i.e. fat) for the measurement of faecal elastase-1, which adds hugely to its practicality and clinical application.

2.2.1.3 Endocrine function: type 3c DM

DM is reported to complicate chronic pancreatitis in 30-50% of patients[88-89]. DM develops due to the loss of Islet cell function, possibly as a consequence of micro-ischemia, and the decrease in the secretion of hormones such as glucose dependant insulinotropic peptide (due to malabsorption of glucose) and glucagon. This type of pancreatogenic DM is referred to as diabetes type 3c, or simply type 3. Whereas the prevalence of types 1 and 2 are well characterised, data on type 3c DM hardly exists[90]. There are distinct differences in the various types of DM. Those with type 3c DM are typically older than those with type 1, but not type 2. They have significantly lower BMI than type 2 patients, possibly attributable to the malabsorptive process in chronic pancreatitis. Hypoglycaemia is common in type 3c DM,

similar to the risk in type 1 DM, which differentiates type 3c from type 2[91]. Poor awareness of the different class of DM may lead to misclassification. A correct classification is nevertheless important, due to the additional therapeutic considerations for this group, not least treatment with PERT[91]. There have been no guidelines to assist on the medical management of pancreatogenic DM. In a review article[92], Cui and Andersen provided some direction on management although there was little focus on nutrition specifically, outside of recommending adequate PERT, vitamin supplementation and lifestyle advice (specifically weight loss in the obese, abstinence from alcohol,l and smoking cessation). The authors however recommended avoiding insulin and insulin secretagogues in type 3c DM related to chronic pancreatitis[92]. The paper discusses pancreatogenic DM as a premalignant condition in which hyperinsulinaemia may enhance the development and growth of pancreatic carcinoma[92]. The authors conceded that these guidelines may be further amended as additional data are published in this emerging sub-area. Dietary management in pancreatogenic DM may be complicated by malabsorption, alcohol abuse and erratic dietary intake[93]. The risk of hypoglycaemia is of particular concern due to the combined effects of alcohol intake, malabsorption, erratic eating patterns and destruction of glucagon producing cells. Therefore, dietary restriction for blood sugar control may need to be less stringent than in type 1 and type 2 DM due to the combined risk of hypoglycaemia and malnutrition.

2.2.2 Malnutrition

2.2.2.1 Body composition

Patients with chronic pancreatitis tend to be thinner than controls. However, there have not been many studies investigating nutritional status or malnutrition in chronic pancreatitis. In a Danish patient group[94], chronic pancreatitis patients with PEI had significantly lower BMI (22(3) kilograms (Kg)/metre (M)^2) than those who were exocrine sufficient (23 (5) Kg/M^2). In an Italian study published in 1997, chronic pancreatitis patients had significantly lower BMI (21.9 (3.1) Kg/M^2) than controls (26.1 (3.1) Kg/M^2). However, the usefulness of BMI is questionable in this group as muscle wasting may occur despite apparently normal (or overweight) body habitus. Therefore measurements which account for muscle and fat mass

are more clinically relevant. More recent data is available from India, Midha and colleagues[45] reported levels on malnutrition in chronic pancreatitis. As well as lower BMI in the chronic pancreatitis group compared to controls (19.4 (3.4) Kg/M^2 *versus* 21.31 (3.69) Kg/M^2), they noted the chronic pancreatitis group had lower mid upper arm circumference (MUAC), triceps skin-fold (TSF), and mid arm fat area (MAFA). A second Indian study[95] compared body composition in alcoholic chronic pancreatitis with that of tropical pancreatitis. They found no difference in BMI, MUAC and TSF between the two aetiologies; although all chronic pancreatitis patients were significantly lower in these measurements than control subjects. Whether or not data from Indian populations can be applied more broadly is unclear.

2.2.2.2 Nutritional requirements and dietary intake

The ongoing disease process in chronic pancreatitis may increase requirement for nutrition. Resting energy expenditure (REE) is higher than normal in chronic pancreatitis by 30-50%. One study found that REE was higher in underweight chronic pancreatitis patients (35$\pm$0.9 kcal/Kg/24 hours) compared to normal weight chronic pancreatitis patients[96]. Non-septic chronic pancreatitis patients may be normocatabolic, compared to septic chronic pancreatitis patients or patients with acute pancreatitis[58]. Consequently, in chronic pancreatitis, a high calorie intake of 35kcal/Kg/24 hours is recommended, although a distinction is not made between those who are septic, underweight or normal weight[5]. Although there appears to be a higher expenditure of energy in chronic pancreatitis, there is also a mechanism whereby the chronic pancreatitis patient can salvage energy from malabsorbed substrates in the colon. This is due to the action of colonic bacteria which act upon the malabsobed carbohydrate as it passes into the colon, yielding energy which may be utilised by the patient. One study demonstrated that 10.2% of energy expenditure/requirement is derived from the salvage of malabsorbed carbohydrate in chronic pancreatitis[85].

Little is known regarding dietary intake in chronic pancreatitis, although it appears that patients do not eat less total calories than controls. From limited data, patients may have a higher carbohydrate intake and fat intake, probably in an attempt to prevent the adverse

effects of fat malabsorption. One small study on 40 male chronic pancreatitis patients found that patients with chronic pancreatitis actually consumed more calories than healthy controls, attributable to a higher carbohydrate intake[97]. Despite the higher calorie intake, the chronic pancreatitis patients had significantly lower body weight, waist circumference, and BMI. Midha *et al* [45] found that while calorie intakes did not differ, overall fat intake, calories from protein, and calories from fat were statistically lower in those with chronic pancreatitis than in controls. They also found that calories from carbohydrate was higher in chronic pancreatitis.

2.2.2.3 The impact of alcohol

Alcohol is a major aetiological factor in chronic pancreatitis, and the ingestion of excess alcohol may be an independent risk factor for malnutrition. Alcoholic individuals are likely to have poor nutrient intakes, either through displacement of food or due to effects on appetite[98]. Alcohol may also cause nutrient malabsorption manifesting as diarrhoea. Reasons for dysfunctions in absorption may be due to impaired or altered biliary or pancreatic function, and direct effects of alcohol in the GI tract[99].

2.2.3 Vitamin deficiency

Historically it was believed that patients with chronic pancreatitis must be deficient in fat soluble vitamins; however although there are clear risk factors (poor diet, malabsorption) the studies which underpin these assertions are few. The theories supporting vitamin deficiency in chronic pancreatitis are reasonable; suboptimal dietary intake affects nutritional status which is exacerbated by increased requirements, antioxidant activity, impaired nutrient binding and malabsorption which greatly augment the risks of deficiency. Despite the theory, the studies which actually describe deficiency of vitamins A and E were published in the 1980's and 1990's. The available literature suggested that vitamin E deficiency in chronic pancreatitis may be as high as 75%[100] but may be sub-clinical rather than overt,[101] although one case study reported neurological manifestations of vitamin E deficiency in a patient with chronic pancreatitis with associated poorly controlled DM[102]. Vitamin E deficiency may be

more prevalent in the presence of steatorrhoea[100-101], malnutrition[103-104] and in alcoholic chronic pancreatitis[104], independent of dietary intake. Deficiency of vitamin E may occur more often than vitamin A deficiency[100-101], and vitamin D and K deficiencies[101]. Vitamin B12 deficiency can occur in chronic pancreatitis due to inadequate protease secretion by the pancreas which is required to release the vitamin for absorption in the terminal ileum[105]. However, vitamin B12 deficiency in chronic pancreatitis appears to be relatively uncommon. There has been more recent research on vitamin D within the last ten years (see section 2.2.4). Chapter 6 of this thesis investigates malnutrition and micronutrient status in chronic pancreatitis.

2.2.4 Osteoporosis and bone health

Patients with chronic pancreatitis are at increased risk of bone demineralisation ultimately leading to osteoporosis and osteopenia. Contributing factors are the malabsorption of vitamin D and calcium, poor dietary intake, smoking and low physical activity. Osteoporosis in particular is a major public health problem if it leads to fracture, with costs in acute hospital care and in nursing home care[106]. The total cost of osteoporotic fractures in England and Wales was estimated at £1.73 billion per year in 2001[107].

2.2.4.1 Vitamin D

Vitamin D is essential for active intestinal calcium absorption, playing an essential role in maintaining calcium homeostasis and skeletal integrity[108]. Lack of sunlight increases the need for dietary sources of vitamin D, which includes infrequently consumed foods such as fatty fish and liver. Foods artificially fortified with vitamin D such as milk and cereals are valuable sources. However, if dietary and sunlight sources are inadequate, there is likely to be a need for supplementation to achieve adequate levels of serum vitamin D. In most cases, deficiency or insufficiency of vitamin D is asymptomatic, although in osteomalacia following prolonged deficiency, skeletal pain and muscle weakness may be present. Biochemically, serum vitamin D, calcium and phosphate may be low, and alkaline phosphatase may be elevated. Hyper-secretion of para-thyroid hormone (PTH) and therefore elevated PTH levels may be one of

the earliest signs of insufficient vitamin D stores. In chronic pancreatitis, vitamin D deficiency is related to the degree of PEI and therefore is more pronounced in severe disease[109]. However, even those with residual exocrine function may have significantly low levels of serum vitamin D and recued bone density[109].

2.2.4.2 Bone health guidelines

Crucially, osteoporosis is a preventable disease. Bone health guidelines for other GI conditions (IBD[110] and coeliac disease[111]) have recommended routine assessment of bone density and calcium/vitamin D supplementation to reduce the risk of osteopathy. However, despite studies reporting a high incidence of osteopathy in chronic pancreatitis[94, 109, 112], no such guidelines exist for chronic pancreatitis. Chapter 7 and 8 investigate bone health in chronic pancreatitis.

2.2.5 Nutritional management of chronic pancreatitis

2.2.5.1 Nutritional requirements

Regarding dietary guidelines, 30% of total calories can be given as fat for patients with chronic pancreatitis. The ESPEN guidelines[56] stated that vegetable fat may be better tolerated (than animal fat), however this was unsupported by a reference, and a literature search yielded no evidence for this assertion. Previously considered appropriate, fat restriction is no longer recommended as it may lead to malnutrition in the already at risk patient[113]. To aid weight gain (if required), particularly where there is co-existent steatorrhoea, supplementation with a medium chain triglyceride (MCT) fat source may be useful. MCTs require minimal digestion and are absorbed even in the absence of pancreatic lipase[114]. However, they may cause cramps, nausea and diarrhoea, and may be unpalatable[5]. MCT intake should be increased slowly according to tolerance[5]. Food sources include coconut oil and palm kernel oil. Commercial products are also available including MCT oil emulsions and EN feeds which contain MCT in preference to long chain triglycerides. A diet rich in carbohydrate and protein is generally advised, although carbohydrate may need to be limited in the case of concurrent DM[56]. A protein intake of 1.0-1.5 g/Kg is sufficient and well-

tolerated[5, 56]. A low fibre diet is generally recommended, as fibre may absorb pancreatic enzymes and thus delay the absorption of nutrients[5, 81]. Frequent meals of low volume and the avoidance of foods that are difficult to digest are recommended[115].

2.2.5.2 PERT

A reduction in steatorrhoea and an adequate energy intake are the most important principles of nutrition therapy in chronic pancreatitis[56]. A study published in 2004 by Dumasy and colleagues found that the annual loss of BMI suffered by chronic pancreatitis patients was higher in those with untreated malabsorption.[116] PERT is usually recommended as exocrine function worsens. However, even those with mild malabsorption without clinical steatorrhoea may experience a negative effect on weight loss.[116] In normal physiological circumstances following a meal, pancreatic enzyme secretion rises quickly to levels of up to six-fold above normal interdigestive levels. Maximum enzyme production is reached at between 20 and 60 minutes post-prandially. Subsequently, enzyme output falls to between 3-4-fold above normal levels, and this is maintained for 3-4 hours before returning to normal inter-digestive levels[115]. There is a mean output of lipase of 2,000-4,000 U/min after ingestion of a normal mixed meal, and a maximal output of 3,000-6,000 U/min[4, 115]. Maldigestion is thought to occur when <5-10% of normal enzyme output is delivered. Expert opinion differs regarding the optimal amount of exogenous enzymes required to adequately treat PEI, but PERT should serve to mimic physiological enzyme patterns. Keller and Layer[4] recommended that a cumulative quality of 25,000-50,000 U of lipase is required duodenally for digestion of a regular meal (5% of 2,000-4,000 U lipase /min required for 240 minutes = 24,000– 48,000 U lipase); however they state that far higher doses need to be administered orally due to the destruction of enzymes. Providing the patient with a variety of enzyme strengths, such as 10,000 U lipase, 25,000 U lipase and 40,000 U lipase, can aid flexibility in treatment. To gauge the adequacy of PERT, a full assessment of symptoms and compliance should be undertaken and doses should be increased until symptoms are controlled. Clinical symptoms of PEI are summarised in Table 2.2[117], although it must be borne in mind that the absence of obvious malabsorption symptoms does not ensure the absence of malabsorption. Gastric acid denatures pancreatic enzymes and therefore enteric-coated varieties which are

dissolved only at higher pH levels may be necessary. Where enteric coated enzymes are not used; acid suppression therapy may be recommended in addition to enzymes to off-set low gastric and duodenal pH which can de-activate lipase[81]. Microsphere capsules are used to ensure passage of enzymes in to the small bowel with the ingested food. Ensuring adequate PERT in patients with chronic pancreatitis may result in improvements in QOL, social functioning and confidence, as well as improving body weight and reducing frequency of defecation.[118] Possible complications[81] associated with the use of PERT include bloating, abdominal cramping, flatulence, and rarely; allergic reactions, hyperuricosuria, folate and iron deficiency, salmonella infection and fibrosing colonopathy[119].

Table 2.2 Clinical symptoms of PEI

Steatorrhoea (pale, floating, oily stools)
Loose, watery stools
Undigested food in stools
Post-prandial abdominal pain
Nausea / colicky abdominal pain
Gastro-oesophageal reflux
Bloating / food intolerance
Malnutrition
Weight loss
Vitamin deficiencies (especially A, D, E, K)
Hypoglycaemia in DM

Adapted from Section 20 (Pancreatic Disease in Adults) from The Parenteral and Enteral and Enteral Nutrition Group of the British Dietetic Association (2013). A Pocket Guide to Clinical Nutrition, 5th Edition[117]

2.2.5.3 Supplementation and nutrition support

2.2.5.3.1 Oral nutritional supplements (ONS)

In most cases, normal food will be sufficient to maintain nutritional status[56] and regular dietetic assessment should be undertaken to ensure adequacy of diet. Where low intake persists despite dietary intervention, ONS may be required. Whole protein supplements may be trialled first, and where tolerance is poor, peptide-based or MCT-enriched supplements could be attempted[56]. A recent RCT compared the efficacy of MCT-enriched commercial supplements with dietary counselling by a dietitian for regular food, for the management of malnutrition for patients with chronic pancreatitis[113]. Subjects were followed up after 3 months. Improvement in anthropometrics (including BMI, MUAC and triceps skinfold, TSF) were seen in both groups. Both groups had significant improvements in dietary intake of calories, fat, carbohydrate and protein. There was a significant decrease in fat excretion and pain in both groups, with no difference between the supplement and diet groups. This RCT demonstrated that both dietary counselling and nutritional supplementation may be equally effective in improving the nutritional status of patients, with commercial supplements being no more efficacious than routine dietetic counselling. There is little evidence to recommend a particular type of supplement over another. Where there is co-existent DM, the contribution of nutritional supplementation to the overall intake should be evaluated and in the case of erratic blood sugar control a lower carbohydrate supplement may improve control.

2.2.5.3.2 EN and PN

Supplemental or total EN may be indicated 1) where the patient cannot ingest sufficient calories (for example due to pain or obstruction), 2) where weight loss continues despite apparently sufficient intake, 3) in the presence of acute complications, such as acute pancreatitis, or 4) prior to surgery[56]. Where long-term feeding is required, a percutaneous endoscopic gastrostomy with a jejunal tube or a direct percutaneous endoscopic jejunostomy could be trialled. About 5% of patients will require EN due to severe and ongoing malnutrition and maldigestion. Long-term jejunal feeding in selected patients may

result in significant weight gain and a decrease in pain, with minimal complications[120]. PN is indicated where EN is not possible (<1% of cases). Indications for PN include gastric outlet obstruction, complex pancreatic fistulae, or severe malnutrition pre-surgery where EN is not feasible[56, 79].

2.2.5.4 Antioxidant therapy

Chronic pain is a major complication for patients with chronic pancreatitis for which there is no effective medical treatment. Pain may be at a debilitating level greatly affecting QOL. There is some evidence that free radical-induced pancreatic damage resulting in intractable pancreatic pain may be alleviated by taking a commercial anti-oxidant preparation (including selenium, beta-carotene, L-methionine, vitamin C and vitamin E). A study published in 2006 investigated the effect of administering an antioxidant preparation containing 75 μg selenium, 3 mg betacarotene, 47 mg d-alpha-tocopherol acetate (vitamin E), 150 mg ascorbic acid (vitamin C) and 400 mg methionine[121]. Results suggested an increase in QOL and a decrease in pain, however the study was limited by small sample size and short duration. A larger placebo-controlled, double-blinded trial of 127 chronic pancreatitia patients investigated the effects of an antioxidant preparation containing 600 μg selenium, 0.54 g of ascorbic acid, 9,000 IU betacarotene, 270 IU alpha-tocopherol, and 200 g methionine[122]. This study demonstrated a significantly greater reduction in painful days per month in those receiving antioxidant therapy compared to placebo. There was also a greater decrease in the requirement for analgesia in the antioxidant group. Furthermore, 32% and 13% of patients became pain-free in the antioxidant and placebo groups respectively. A reduction in pain had the important effect of reducing work-days lost. The benefits were seen after only 3 months. A significant increase in blood antioxidant levels was demonstrated in the antioxidant group. However, Siriwardena *et al* published results in 2012 which contradicted the putative benefits of antioxidants in chronic pancreatitis. As part of the ANTICIPATE (ANTI-oxidant therapy for painful Chronic Pancreatitis Therapy Evaluation) trial they recruited 92 eligible patients with chronic pancreatitis of which 70 patients completed the study. Thirty-three patients received antioxidant therapy and 37 received placebo. Despite demonstrating an

increase in blood antioxidant levels, they did not show an increase in QOL, nor a reduction in pain in an antioxidant-treated groups compared to placebo[123].

2.2.6 Conclusions

Nutrition in chronic pancreatitis has been described as a 'problem area'.[124] Many gaps exist regarding optimal nutrition management in chronic pancreatitis including the need to properly characterise malnutrition, body composition, dietary intake, vitamin deficiency and bone health. Limited data indicate that malnutrition is prevalent, with fat soluble vitamin deficiency and osteoporosis being particular concerns. Focus on nutrition-based research for chronic pancreatitis is required to inform clinical practice and ultimately prevent long-term complications, improve nutritional status and enhance QOL.

Chapter 3 Thesis outline, rational, and aims

This chapter will describe the background to this body of work, along with the rationale and specific objectives of each study

3. 1 Thesis context

In recent years the nutritional management of acute pancreatitis has evolved considerably due to the volume of international research on the topic. An increase in research led to the development of many international consensus guidelines as discussed in Section 2.1.7. However, basic controversies which represent obstacles to practice still exist. The acute pancreatitis research element of this work developed from a need to evaluate current clinical practice compared to the many available guidelines. Conversely, compared to acute pancreatitis, little had changed in the dietetic management of chronic pancreatitis in the years preceding these studies, likely due to lack of nutrition-based research in chronic pancreatitis. Consequently, there is a considerable gap in the evidence-base regarding nutritional management, and therefore chronic pancreatitis is the lesser-discussed disease within published consensus guidelines. Despite this, indications from the limited available studies suggest that malnutrition and deficiencies are not uncommon. The chronic pancreatitis research element of this thesis arose from a need to identify and define nutritional concerns in chronic pancreatitis. Of particular interest were the characterisation of malnutrition and the investigation of nutrient deficiency. As initial work identified bone health as a concern, the final portion of the thesis examines bone metabolism in chronic pancreatitis. Figure 3.1 illustrates the published research in both disease subgroups, and the resultant gap in the knowledge which has driven this research.

3.2 The Heath Research Board training fellowship

This work is funded by the Health Research Board (HRB), Ireland by means of a health professional's fellowship. The HRB stipulated that output must have an emphasis on clinical research and service, improved clinical knowledge, improved critical thinking/ research skills, professional development, and lead to innovations in health and social care. Findings must

have a realistic potential of being applied in practice and have relevance to health and social gain. Finally, the fellowship is a personal research training fellowship and not just a means of funding a project. Bearing these criteria in mind, this work was inherently patient-orientated, focusing on topics that had a real opportunity to effect change in the clinical management of patients with pancreatitis. In particular, emphasis was placed on the production/development of clinical guidelines. While the initial studies examined practice in this institution, and later internationally, the latter studies arose from a need to broaden the scant research-base. As a fellowship with an emphasis on personal research training and research application, the author focused in particular on dissemination of results and alignment with international peers and professional bodies.

3.3 Thesis outline

In acute pancreatitis, 3 studies, which were undertaken to evaluate clinical practice both locally and internationally, are described in Chapter 5. For chronic pancreatitis, an evaluation of clinical practice would have been neither feasible nor useful, given the lack of guidelines against which practice could be measured. Therefore, this led to the design of a cohort study to investigate malnutrition and deficiency in patients with chronic pancreatitis. This study had two broad themes: malnutrition and bone health. Chapter 6 details the findings of the investigation into malnutrition and deficiency in chronic pancreatitis, while Chapter 7 describes the findings of the bone health work. As osteoporosis was found to be a particular concern for patients with chronic pancreatitis based on this first cohort study, a systematic review and meta-analysis was conducted and is described in the second part of Chapter 7. In addition, a second cohort study was designed, with the aim of further assessing the prevalence of osteoporosis, investigating bone metabolism and evaluating the association between bone turnover and systemic inflammation. This study is described in Chapter 8. Figure 3.2 illustrates the thesis outline and evolution of studies.

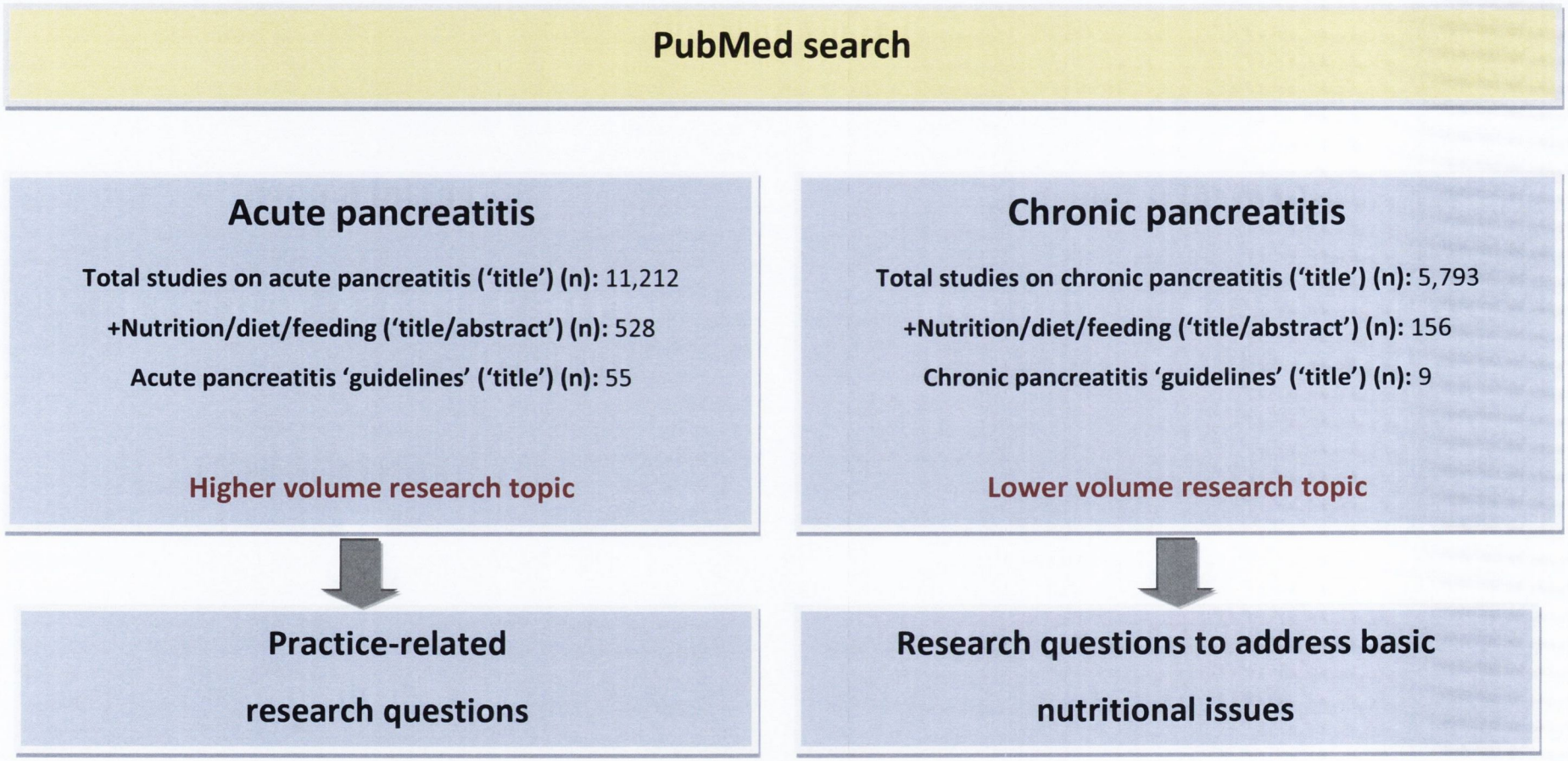

Figure 3.1 Studies identified from a PubMed search on acute and chronic pancreatitis

The above figure illustrates the imbalance in research between acute and chronic pancreatitis. Search conducted: July 2010

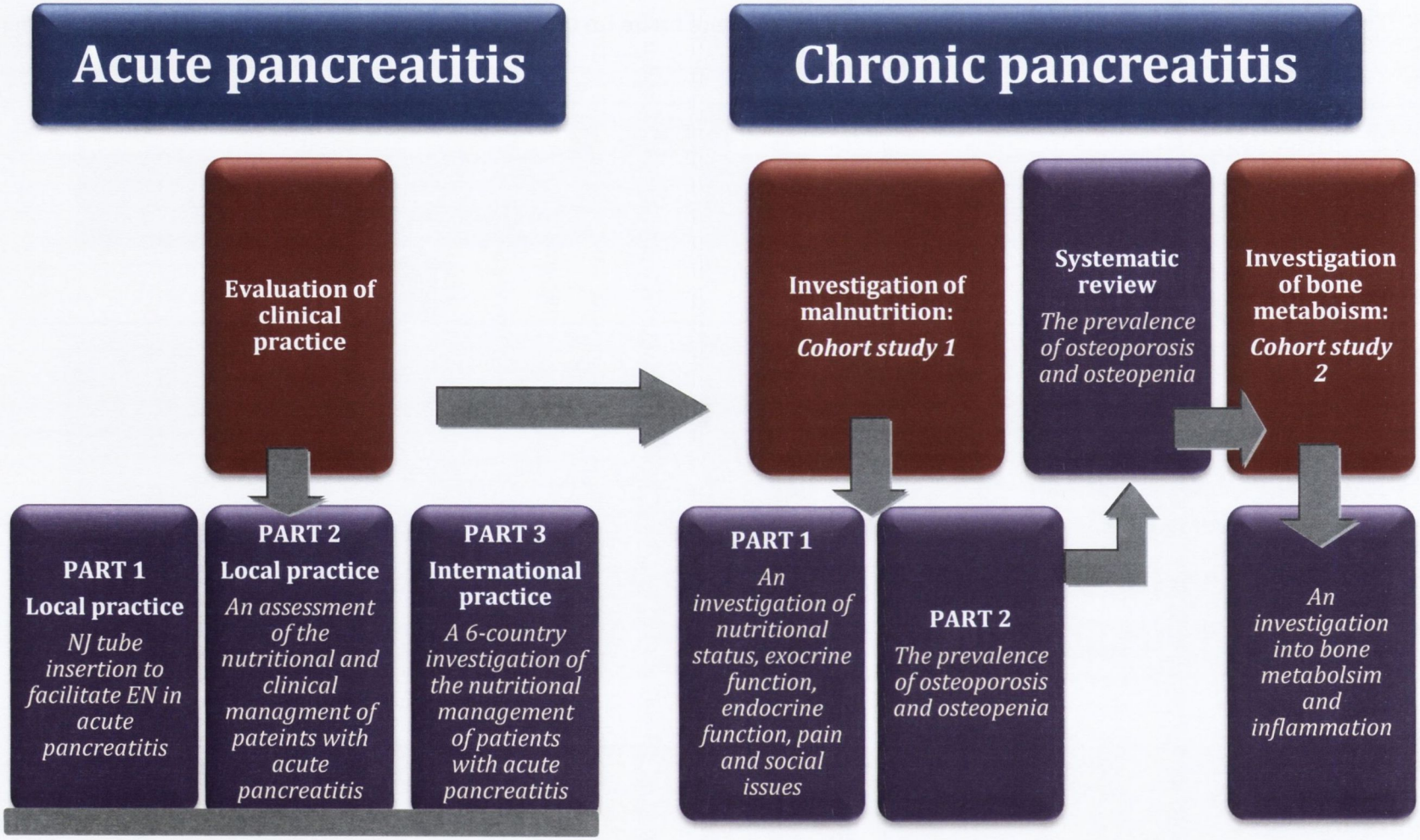

Figure 3.2 Outline of thesis studies

3.4 Overall thesis aims

These studies had two broad aims, displayed in Table 3.1.

Table 3.1 Broad thesis aims

Research question 1 **How does nutritional practice in acute pancreatitis compare to published guidelines?**
Objective 1 To investigate whether NJ feeding tubes can be safely inserted by bedside ***Objective 2*** To compare local clinical practice in acute pancreatitis to published guidelines ***Objective 3*** To investigate international nutritional practice in acute pancreatitis compared to published guidelines
Research question 2 **What is the nutritional status of patients with chronic pancreatitis compared to controls?**
Objective 4 To examine malnutrition, nutrient deficiency, adverse symptoms and pancreatic function in patients with chronic pancreatitis ***Objective 5*** To examine the prevalence of osteoporosis and osteopenia in chronic pancreatitis ***Objective 6*** To conduct a systematic review and meta-analysis of the prevalence of osteoporosis and osteopenia in chronic pancreatitis ***Objective 7*** To investigate the association between biochemical markers of bone metabolism and systemic inflammation in chronic pancreatitis

Chapter 4 General methodology

General methodology is detailed here including details on the investigator, aims and objectives, ethical approval, study design, setting, recruitment, questionnaires, assessment and statistical analysis. Specific details pertaining to individual studies are provided in the relevant chapters.

4.1 Investigator and data collection

The author of the thesis conducted all aspects of the literature reviews, design, data collection (using face-to-face interviews), data entry, statistical analysis and writings detailed within this thesis. Assistance was provided in some instances:

-For the international audit (Chapter 5, Part 3), the data was collected electronically following dissemination by the author *via* key dietetic contacts and groups.

-The author was assisted in conducting the systematic review (Chapter 7) by a second independent reviewer, clinical dietitian Niamh D. Smyth.

-Christina M. Purcell (research dietitian) assisted with patient recruitment and database set-up for the second cohort study (bone metabolism, Chapter 8). Data was collected using face-to-face interviews.

-Assistance was provided by a statistician for analysis within Chapter 7.

For all studies and methodologies, the thesis supervisors provided guidance and support.

4.2 Ethical approval

4.2.1 Informed consent

Where applicable, ethical approval was sought for individual studies from the joint Tallaght Hospital / St James Hospital ethics committee. Letters of approval are provided in Appendix D. Informed verbal and written consent was obtained in all cases and subjects were furnished with written information on procedures and assessment particulars and provided with time to consider before signing. Relevant contact details were also supplied. Subjects

were informed of their right to refuse to participate and their right to withdraw from the study. Patients were assured that this would in no way influence their nutritional or medical care.

4.2.2 Data storage

Confidential patient notes and charts were stored in locked rooms within the Trinity Centre for Health Sciences (research offices) to which only the author and those involved in the studies had access. Electronic information was stored under confidential passwords. Swipe-card access was required to gain access to the Trinity Centre from the main hospital. Data analysis was done in the Trinity Centre for Health Sciences or in the Department of Nutrition & Dietetics, both located at Tallaght Hospital. All data were treated as confidential and never disclosed to a third party.

4.2.3 Vulnerable subjects

Children were not included in the studies. Intellectually impaired adults, those with brain injuries or otherwise incapacitated adults were not included. Where staff members were recruited as controls, participation was voluntary and first contact was made by the subject by means of a telephone call or email in response to study advertisements. Women of child-bearing years were included. In the case of bone density assessments by dual X-ray absorptiometry (DXA) (Chapters 7 & 8), due to the potential risk of radiation exposure, a strict window of 'within 10 days of the last menstrual period' was strictly enforced in accordance with the policies of the Department of Radiology, Tallaght Hospital.

4.2.4 Study sponsorship

The studies herein were funded by the HRB which did not exert constraints over the studies. Similarly, the Meath Foundation who provided a seed grant for early pilot clinical studies did not exert constraints on the studies. No commercial entities were involved in sponsorship or otherwise. Neither the author nor the other investigators involved in the studies had any conflicts of interest.

4.3 Study design

To achieve the aims of the thesis, several methodological and scientific approaches were employed for which specific details are described in the relevant study chapters (Chapters 5-8). General approaches are outlined below. The studies were conducted between September 2008 and March 2013.

4.3.1 Study setting

All patient-related studies were conducted in the Centre for Pancreatico-Biliary Diseases, Tallaght Hospital (Formerly Adelaide & Meath incorporating the National Children's Hospital), and all patients were recruited from this institution with the exception of the bone metabolism study (Chapter 8), for which patients from St. Vincent's University Hospital were also recruited. As Tallaght Hospital is a tertiary referral centre for pancreatic disease, the patients resided throughout Ireland. The Centre for Pancreatico-Biliary Diseases treats up to 170 pancreatitis patients per year.

4.3.2 Recruitment

4.3.2.1 Patients

Patients were recruited by one of three means:

1. Patients presented to The Centre for Pancreatico-Biliary Diseases, Tallaght Hospital
2. Patients presented to another medical speciality within Tallaght Hospital and were referred by the medical team
3. Patients were identified by the data-base coordinator from the departmental pancreatic database

4.3.2.2 Controls

Controls were recruited by advertising within Tallaght Hospital (specifically targeting staff) by means of posters and emails to specific departments. Further controls were recruited from businesses adjacent or in proximity to Tallaght Hospital and were obtained through contact with human resources departments, posters and word of mouth.

4.3.2.3 Incentivisation

Participation was voluntary and no payment (monetary or otherwise) was provided, nor were expenses reimbursed. However, all costs associated with assessment or procedures relevant to the study were met by the department and no payment for tests or otherwise was sought from patients or controls.

4.4 Questionnaires

Questionnaires and data collection forms specific to the various studies are discussed within the individual study chapters, and are included in the Appendices.

4.5 Assessment and equipment

General measurements are detailed here. Further details and reference ranges are provided within the specific chapters if appropriate.

4.5.1 Biochemistry

Blood samples from study participants were taken by the Phlebotomy Department of Tallaght Hospital and were processed and analysed at the Tallaght Hospital Biochemistry Department according to standard protocols. Where applicable, samples were sent to St James Hospital, Dublin (fat soluble vitamins, Chapters 6 & 7) and St Vincent's University Hospital, Dublin (bone metabolism, Chapter 8). Tables 4.1 and 4.2 summarise the biochemical assays used in this research and include the assessment of standard, nutritional, bone, and inflammatory markers.

4.5.2 Faecal samples

To assess pancreatic function, faecal samples were sent to the Biochemistry Department of Tallaght Hospital for preparation and from there shipped to the Biochemistry Department of the University Hospital of South Manchester (UK) for faecal elastase-1 analysis using enzyme-linked immunosorbant assay (ScheBo® Pancreatic Elastase-1 Stool Test, Germany, Figure 4.1), expressed as µg / g stool (Chapters 6 & 7). See Table 4.3 for faecal elastase-1 reference ranges.[125]

Figure 4.1 ScheBo® Pancreatic Elastase-1 Stool Test

Table 4.1 Details of biochemical assays, reference ranges and sites of analysis

	Unit	Method of measurement	Range	Site	Chapter
CRP	mg/L	Immunoturbidometric assay	0-5	TH	4,6,7
PTH	pg/ml	Solid-phase 2-site chemiluminescent enzyme-labeled immunometric assay	12-65	TH	7,8
Glucose	mmol/L	Enymatic reference method with hexokinase		TH	6,7
HbA_{1c}	%	Reversed-phase cation exchange chromatography		TH	6,7
Vitamin D (25-OH D)	nmol/L	Liquid chromatography-tandem mass spectrometry	< 25 deficient < 80 insufficient	SJH	6,7,8
Vitamin A (retinol)	µmol/L	High performance liquid chromatography	1.6-3.7	SJH	6
Vitamin E	µmol/L	High performance liquid chromatography	21.3-43.8	SJH	6
Vitamin E:lipid ratio	µmol/L		3.8-6.3	SJH	6
OC	ug/L	Sandwich immunoradiometric assay	9.5-22.2	SVUH	8
P1NP	ug/L	Radioimmunoassay	27.2-71	SVUH	8
CTX-1 (β CrossLaps)	ug/L	Solid-phase 2-site chemiluminescent enzyme-labeled immunometric assay	0.016-0.584	SVUH	8
Testosterone	nmol/L	Electrochemiluminescent immunoassay	8-31 (male)	TH	8
FSH	U/L	Electrochemiluminescent immunoassay	**	TH	8
LH	U/L	Electrochemiluminescent immunoassay	**	TH	8
Oestradiol	pmol/L	Electrochemiluminescent immunoassay	**	TH	
IL-6	pg/mg	Solid phase ELISA quantitative sandwich enzyme immunoassay	Expected normal value <3 pg/ml	TH	8
IGF-1	nmol/L	Sandwich chemiluminescent (IDS iSYS)	*	TH	8
TNF-α	pg/mg	Solid phase ELISA quantitative sandwich enzyme immunoassay	Expected normal value <15 pg/ml	TH	8
hsCRP	mg/L	Particle-enhanced immunoturbidometric assay	0.07-1.8	TH	8
TSH	mU/L	Electrochemiluminescent immunoassay	0.3-4.2	TH	8
Free T4	pmol/L	Electrochemiluminescent immunoassay	12-22	TH	8

CRP C-reactive protein, PTH para-thyroid hormone, TH Tallaght Hospital, SJH St James Hospital, SVUH St Vincent's University Hospital, 25-OH D, OC osteocalcin, P1NP aminoterminal propeptide of type-1 collagen, CTX-1 carboxy-terminal telopeptide of type 1 collagen, FSH follicular stimulating hormone, LH luteinising hormone, IL interleukin, IGF insulin growth factor, TNF tumour necrosis factor, TSH thyroid stimulating hormone
* Age and sex-specific (see Table 4.2), ** Cycle-specific

Table 4.2 LH, FSH and oestradiol institutional reference ranges (Tallaght Hospital Biochemistry Department)

	Follicular	Midcycle	Luteal	Menopause
FSH	<13	<20	<8	>25
LH	<13	<95	<11	>55
Oestradiol	45-600	300-1800	160-780	<200

Table 4.3 Reference ranges for pancreatic faecal elastase-1

Results	Interpretation
> 200 mcg/g	Normal / rules out significant pancreatic dysfunction
100-200 mcg/g	Suggests mild to moderate PEI
<100 mcg/g	Reflect moderate to severe PEI

Pancreatic Elastase 1 Stool test Kit Insert. Schebo Biotech AG. Glessen, Germany, 2005 June[125]

mcg micrograms

4.5.3 Anthropometry

4.5.3.1 Weight, height and body mass index (BMI)

Height was measured using a stadiometer (Holtain Ltd., Crywych, Dyfed, UK) (Figure 4.2). Weight was measured with subjects wearing light clothes and without shoes using a calibrated Seca 708 weighing scale (Seca, UK) (Figure 4.3). BMI was calculated as weight (Kg) divided by height (M^2) and was classified according to the WHO classification[126] (Table 4.4).

Table 4.4 WHO classification of obesity

WHO class	Body Mass Index Kg/M^2
Underweight	<18.5
Normal weight	18.5-24.9
Overweight:	
Pre-obese	25.0-29.9
Obese class I	30.0-34.9
Obese class II	35.0-39.9
Obese class III	>40.0

Figure 4.2 Holtain stadiometer

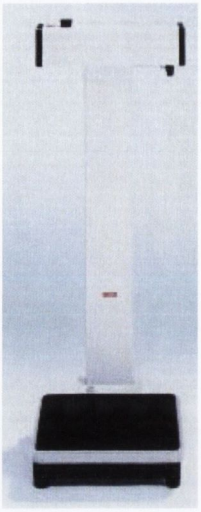

Figure 4.3 Seca 708 weighing scale

4.5.3.2 Body composition

To measure muscle mass, mid arm muscle circumference (MAMC) was constructed from MUAC and TSF. MUAC was measured on the right side of the body, with the arm relaxed by the patient's side. Firstly, the midpoint was identified with the arm at a 90 degree angle and the palm faced upwards. The midpoint was obtained between the acromial process of the scapula and the olecranon process[127] (Figure 4.4). TSF (a measure of body fat) was done using Lafayette Skinfold Calliper II (Lafayette Instrument, UK) and expressed in mm. TSF was measured on the right side of the body, with the arm hanging relaxed at the patient's side. The skin fold was measured at the midpoint as before, over the triceps muscle and measured to the nearest millimetre, 2-3 seconds after applying the calliper. The average of three measurements was taken (Figure 4.5). Values were compared to original reference guides published by Bishop and colleagues[127] for both sexes separately. MAMC was calculated from MUAC and TSF using the following equation:

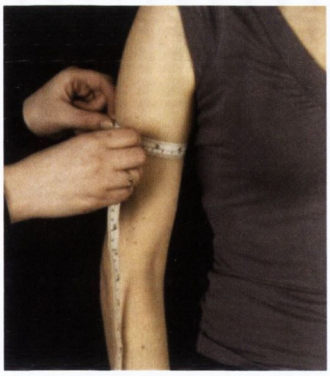

Figure 4.4 Measurement of MUAC for the calculation of MAMC

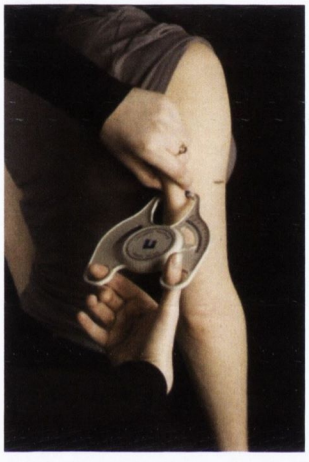

Figure 4.5 Lafayette Skinfold Calliper II

Figure 4.6 Jamar handgrip dynamometer

4.5.3.3 Handgrip strength

Handgrip strength was measured using a Jamar Handgrip Dynamometer and expressed in Kg (Figure 4.6). The mean of 3 attempts were calculated according to standard protocols.

4.5.4 Bone density assessments

Bone density for study participants was assessed in the Tallaght Hospital Radiology Department using a Lunar Prodigy Advance densitometer, software version 11.40 (GE healthcare, GE Medical Systems, Belgium) (Figure 4.7). DXA (bone density assessment) was conducted by a radiographer and results reported by a Consultant Radiologist who was blinded to the underlying condition. Results were expressed as T-scores compared to the values of young females (representative of 'peak bone mass')[128] (Table 4.5). Diagnosis of osteoporosis or osteopenia was determined by the consultant Radiologist using the lowest T-score at any area. Further details for bone density assessment are provided in chapters 7 and 8.

Figure 4.7 Lunar Prodigy Advance Densitometer

Table 4.5 WHO diagnostic categories relating to normal or low bone density values

Diagnosis	Categories	T-score
Normal bone density	A value of BMD or BMC less than 1 SD below average*	> - 1
Osteopenia	A value of BMD or BMC between 1 SD and 2.5 SD below average*	-1 to -2.5
Osteoporosis	A value of BMD or BMC more than 2.5 SD below average*	<-2.5
Severe osteoporosis	Fragility fractures and a value of BMD or BMC more than 2.5 SD below average*	<-2.5

SD standard deviation

* Average value is that of young adults

4.5.5 Assessment of severity of acute and chronic pancreatitis

The modified Imrie score[129] was used (along with CRP) to determine the severity of acute pancreatitis and is detailed in Table 4.6. The Cambridge classification[130] which was used to stratify patients with chronic pancreatitis according to severity is detailed in Table 4.7. Both are recognised tools for the assessment of disease severity.

Table 4.6 Modified Imrie Score (Glasgow Score) for the determination of severity in acute pancreatitis

Age > 55 years
WBC count > 15 × 109/l
Blood Glucose > 10 mmol/l
Blood Urea > 16 mmol/l
Arterial oxygen partial pressure <8.0 kPa
Serum Albumin < 32 g/l
Serum Calcium < 2.0 mmol/l
Lactate Dehydrogenase > 600 U/l
Data within 48 hours of attack
Score 1 point if factors are present
A score of >3 indicates severe acute pancreatitis
A score of <3 indicates mild acute pancreatitis

WBC white blood count

Table 4.7 Cambridge classification for disease severity in chronic pancreatitis

Score 1 (Cambridge class 0) - Severity: normal - Good quality ERCP/ US or CT visualising whole gland without abnormal signs **Score 2 (Cambridge class 0)** - Severity: equivocal - ERCP: <3 abnormal branches - US/CT: abnormal sign: main pancreatic duct 2 to 4 mm diameter, gland 1 to 2 x normal **Score 3 (Cambridge class I)** - Severity: mild - ERCP: 3 or more abnormal branches - US/CT: 2+ abnormal signs: cavities <10 mm, duct irregularity, focal acute necrosis, parenchymal heterogeneity, increased echogenicity of duct wall, contour irregularity of head/body. **Score 4 (Cambridge class II)** - Severity: moderate - ERCP: >3 side branches plus abnormal main duct - US/CT: as score 3 **Score 5 (Cambridge class III)** - Severity: severe - ERCP: all of above, plus 1 or more of: large cavity >10 mm, intraductal filling defects, duct obstruction (stricture), duct dilation or irregularity - US/CT: all of above, plus 1 or more of: large cavity >10 mm, intraductal filling defects, duct obstruction (stricture), duct dilation or irregularity, calculi/pancreatic calcification, contiguous organ invasion.
The Cambridge classification grades the severity of pancreatic structural changes based on abnormalities of the main pancreatic duct and side branches

ERCP endoscopic retrograde cholangiopancreatography, US ultrasound

4.6 Follow-up of patients and aftercare post study participation

Where nutritional or bone health measurements were assessed, results were sent to the patient, to the consultant (for filing in the medical chart), and (with patient consent) to the patient's General Practitioner for follow-up if applicable. For control participants, results were sent to them and to their General Practitioners for follow-up if applicable. An example of the standard results letters sent is provided in Appendix E.

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4.8 Statistical analysis

The author performed all statistical analyses with assistance and guidance where required. The software packages utilised were Minitab (version 15.1, State College, PA, USA) and Comprehensive Meta-Analysis (version 2.2.064, USA), running on a Trinity College-affiliated Dell personal computer. Specific details of statistical analysis are detailed in the individual chapters. In all cases (unless otherwise specified) a P value of <0.05 was taken as statistically significant. Statistical assistance was provided for specific analyses in Chapters 7 and 8 by statisticians from the Centre for Support and Training in Analysis and research (C-STAR, Dublin), as well as by expertise within the Centre for Pancreatico-Biliary Diseases.

Chapter 5 An assessment of the nutritional management of patients with acute pancreatitis

This chapter describes a three-part study which examined the nutritional management of patients with acute pancreatitis (Figure 5.1):

Part 1 describes a study examining the feasibility of blind bedside insertion of small-bowel feeding tubes.

Part 2 describes an audit of the nutritional management of patients with acute pancreatitis presenting to the Centre for Pancreatico-Biliary Diseases over a 3 year period.

Part 3 describes an international survey across six countries which investigated nutritional practice in acute pancreatitis compared to the available management guidelines

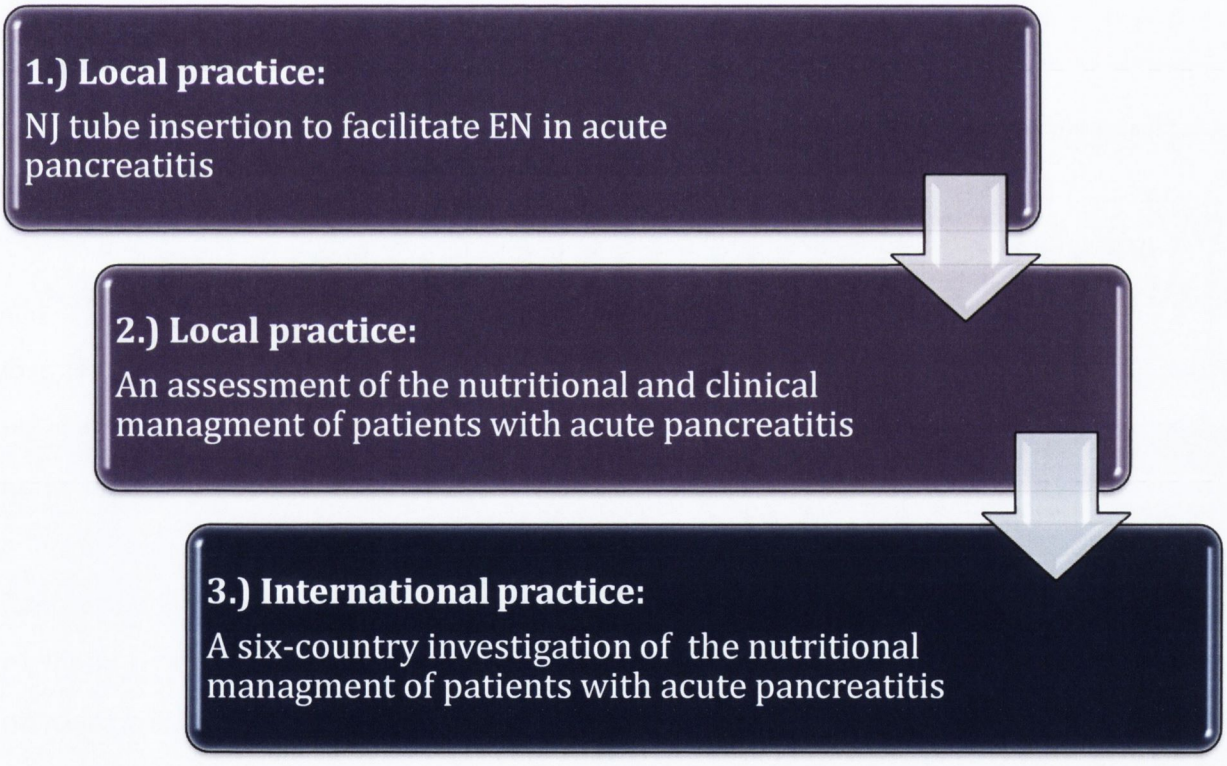


Figure 5.1 Overview of studies in Chapter 5

5.1 General introduction

5.1.1 Feeding in acute pancreatitis

Patients with acute pancreatitis may develop mild or severe disease, with local or systemic complications. In mild disease, recovery is usually self-limiting and uneventful, with patients usually recommencing oral diet within a few days[55-56]. In severe disease, SIRS may develop along with multi-organ failure in some cases. Clinical management of this group focuses on treatment of systemic complications with surgical or drainage procedures undertaken if deemed appropriate. Patients tend to be highly catabolic and develop malnutrition rapidly. A wealth of research in the last 10-15 years has changed nutritional practice in patients with acute pancreatitis.

Although previously considered optional, artificial nutrition support is now considered essential in severe acute pancreatitis.[18, 55-56] For example, nutrition support was not mentioned in the 1998 UK working group guidelines on acute pancreatitis[131], but has been recommended by several expert groups since then.[18, 55-56, 78-79] Similarly, PN was once regarded as the optimal feeding method as it allows delivery of nutrition whilst resting the pancreas; however, systematic reviews of the literature have shown that EN is not only possible, but preferable to PN[60-61, 132].

A more recent controversial issue was discussed in Chapter 2, and relates to whether feeding should be administered gastrically or into the small bowel, the latter having the aim of preventing stimulation of the injured pancreas. In theory, feeding into the stomach (or duodenum) should be harmful as the presence of nutrients will stimulate exocrine secretion by the inflamed pancreas, In practice, vomiting or high gastric residuals are often a complicating feature rendering gastric feeding impossible. In the absence of definitive data, and particularly for patients with severe cases of acute pancreatitis, it seems prudent to deliver feed distal to the stimulatory zone. Clearly, further multicentre, randomised trials are required to determine the ideal route of EN, particularly in the most severely ill acute pancreatitis patients.

The optimal timing of feed commencement brings yet more uncertainty, with the guidelines recommending 'early feeding' but failing to define this in terms of days or hours. A

systematic review[76] on the timing of feeding in acute pancreatitis yielded studies that were not designed to investigate the problem, and therefore are of limited use. Nevertheless, the best evidence available suggests that feeding should be started less than 48 hours after presentation[76]. Regarding which EN formula to use, the ESPEN guidelines stated that while peptide feeds are known to be safe, standard feeds should be tried if tolerated[56]. The latest ASPEN recommendations suggested that tolerance might be improved by using either peptide-based, MCT-based, or fat free formulations[78]. The lack of clarity is again due to inadequate studies. The only systematic review on the topic suggested that peptide feeds are not indicated, however, the quality of the studies included were questionable and more research is required.

5.1.2 NJ feeding

NG feeding is a simple mode of feeding, and is easy to initiate and relatively cost-effective. However, NJ feeding may arguably be more appropriate for those with severe disease. Timely placement of feeding tubes for patients who are hypermetabolic and at high risk of malnutrition is a crucial part of treatment. However, NJ feeding is limited due to the logistical difficulty in placing the tubes past the pyloric sphincter. Traditionally, NJ tubes were inserted in the endoscopy or radiology departments with significant delays, staff requirements and utilisation of hospital resources. Alternative methods of NJ tube insertion have been developed to reduce reliance on endoscopy and radiology departments, including the 10,10,10 protocol – a method for blind insertion of small bowel feeding tubes by the patient's bedside. This procedure was first described by Lord *at al*[133], but was best described by Taylor and Schallom[134]. In 2007, an NJ tube placement protocol was developed by our department based on the 10,10,10 protocol (see Appendix F). The purpose of this initiative was to allow for the timely insertion of NJ tubes in patients with severe acute pancreatitis, and to reduce the costs associated with traditional insertion methods.

5.1.3 Clinical standards and guidelines for nutrition in acute pancreatitis

There has been a plethora of research in acute pancreatitis in recent years, yet despite this, basic controversies still exist regarding how best to manage the nutritional requirements of patients. To provide some direction, management guidelines have been published by various expert groups regarding the appropriate provision of EN and PN. The main international nutrition societies have published guidelines over the last 10-15 years. ESPEN published 'general' pancreatitis nutrition guidelines in 2002[55], followed by EN- and PN-specific guidelines in 2006[56] and 2009[79] respectively. ASPEN published updated guidelines in 2009[78]. In addition, several societies published general pancreatitis guidelines with minor nutrition components: the UK guidelines for the management of acute pancreatitis[18] were published in 2005 by the UK Working Party on Acute Pancreatitis; Practice Guidelines in Acute Pancreatitis[26] were published by the Practice Parameters Committee of the American College of Gastroenterology; and the AGA published a Technical Review on Acute Pancreatitis[17]. However, the existence of such guidelines provides no guarantee of adherence, and therefore, a system of self-monitoring must exist to ensure appropriate practice. The UK guidelines specifically emphasised the importance of clinical audit and recommended that the managing team should maintain regular and prospective audits of all patients with acute pancreatitis[18].

5.1.4 Study rationale and objectives

This chapter describes a three-part study of nutrition support practices in acute pancreatitis.

5.1.4.1 Part 1: The blind bedside insertion of NJ tubes

A high volume of acute pancreatitis patients required feeding *via* NJ tube, the placement of which carry significant implications on cost, specialist staff, time and waiting lists. Patients frequently experienced delays in feeding commencement and prolonged hours of missed feeding. Part 1 of this study describes the evaluation of blind bedside tube insertion. The objectives of this study were:

- To investigate the feasibility and safety of the bedside NJ tube insertion process

- To investigate the cost savings of the NJ insertion process compared to existing insertion methods

5.1.4.2 Part 2: A three-year audit of nutrition support in acute pancreatitis

Depending on disease severity, patients with acute pancreatitis may require artificial nutrition support which may be provided as EN or PN; and for EN, via the gastric or jejunal route. Those deemed to require feeding usually have the most severe form of acute pancreatitis with associated higher risk of complications and death. Several international guidelines have been published to guide the management of acute pancreatitis. As part of this thesis, a study was designed which aimed to retrospectively review a prospectively-maintained nutritional database of acute pancreatitis. The dual objectives of this study were:

- To describe local nutrition support practices in Tallaght Hospital involving the use of EN or PN in patients with acute pancreatitis
- To compare the local practice to published standards

5.1.4.3 Part 3: A transatlantic survey of the nutritional management of acute pancreatitis

General adherence to nutritional pancreatic guidelines is unknown, despite the availability of many management guidelines from several prominent international committees and societies. Part 3 of this study investigated the *international* nutritional management of acute pancreatitis, in the context of the available guidelines.

The study objectives were:

- To describe current international nutrition support practices in acute pancreatitis
- To compare practice between countries and institutions types
- To examine pancreatic teams and protocols, the timing of feeding, EN and PN, feeding routes, requirements, formulae and specific nutrient additions

5.2 Part 1: The blind bedside insertion of NJ tubes

5.2.1 Methods

5.2.1.1 Subjects

A 12 month period up to March 2008 was selected for retrospective evaluation. The records of patients who had had NJ tubes inserted for post-pyloric feeding were sought. Patients for whom there had been at least one attempt at bedside NJ insertion via the 10,10,10 method were included. Insertion details which had been prospectively recorded were available for evaluation: diagnosis, indication for tube, use of sips of water, use of metoclopramide, and success / failure. The time taken to insert the tubes was recorded, as was the occurrence of any adverse events.

Figure 5.2 Corflo fine bore naso-jejunal feeding tube

5.2. 1.2 NJ tube insertion

The procedure used for NJ tube insertion is detailed in Appendix F. Briefly, following administration of metoclompramide, an NJ tube (Corflo®, 8-French, unweighted, 140cm, UK, see Figure 5.2) was inserted into the stomach and gastric placement confirmed. The tube was advanced by 5-10 cm and the guidewire was pulled out of the end of the tube to

determine if the tube was advancing and not coiling / kinking in the stomach. The tube was further advanced and the process repeated by continuously checking the guidewire. When the tube was believed to be in the small bowel, the position was confirmed by obtaining an aspirate (pH > 6.0). Radiological imaging confirmed position (Figure 5.3).

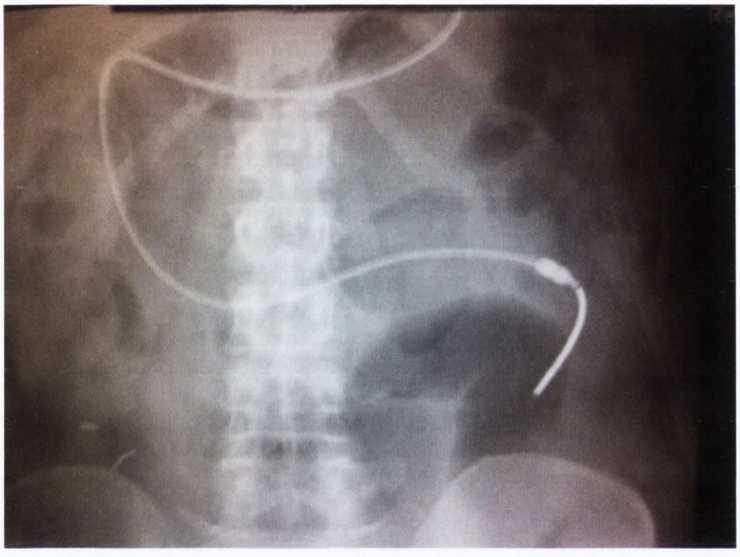


Figure 5.3 Plain film of the Abdomen (PFA) showing correct S-shaped placement of a NJ feeding tube past the pyloric sphincter and into the jejunum

5.2.1.3 Calculation of costs

Costs were calculated for the bedside procedure and were compared to costs for a comparable endoscopy insertion. This data was obtained from the finance and endoscopy departments of Tallaght Hospital and pertained to the study period. For bedside insertion, a dietitian (senior grade) and nurse (clinical nurse specialist grade) were calculated and an average cost obtained for 30 minutes. The portering transfer costs for 30 minutes (transfer of the patient to Radiology for PFA) was included, as well as PFA cost, NJ tube and other equipment. For endoscopy costs, a 30 minute procedure was considered, as well as the cost

of 3 nurses for 30mins and associated equipment costs. For salaries, the midpoint of the salary scale was used.

5.2.2 Results

5.2.2.1 Subjects

A detailed breakdown of study subjects is given in Table 5.1. Twenty-two patients had 37 attempted blind tube insertions. One patient had 6 insertions, 1 patient had 3 insertions, 4 patients had 2 insertions and 15 patients had 1 insertion. There were more males than females and the median patient age was 61 years (range 25-83 years). The most common indication for post-pyloric feeding was severe acute pancreatitis.

5.2.2.2 Insertion details

The 10,10,10 insertion protocol was adhered to in all cases. Metoclopramide (10 mg) to aid passage of the tube into the small bowel was administered in all cases. Patients were able to take sips of water to aid tube insertion in the majority of cases (68%). For two patients the procedure was abandoned; due to agitation (n = 1) and desaturation (n = 1). The clinical nurse specialist allied to the pancreatico-biliary service inserted over half of the tubes (54%). Over a third (35%) were inserted by the pancreatico-biliary service senior dietitian and the remainder by ward nursing staff or by medics. The mean time to insertion where recorded (n = 29) was 33 minutes, including preparation time and insertion time. There were no adverse events or outcomes excepting the two patients for whom the procedure was abandoned.

5.2.2.3 Success rate and costs

The insertion success rate was 91% (32 successful insertions in 35 PFA scans reviewed). However, accounting for abandoned procedures, the overall success rate was 86.5% (32 successful insertions in 37 overall attempted insertions) (Figure 5.4). The mean cost of tube insertion by a senior dietitian or clinical nurse specialist was estimated at € 90.50. This was

substantially lower than the estimated cost of endoscopic insertion (€ 351.55) (Table 5.2). This equates to an overall saving of € 8,353.60 for the 32 successful insertions in this study.

Table 5.1 Characteristics of patients included in the study

	n	%
Gender		
Male	29	78
Female	8	22
Location		
Ward	27	75
Intensive Care Unit	10	25
Age (*n* = 22)		
<25 years	1	5
26-49 years	6	27
50-75 years	13	59
>75 years	2	9
Indication		
Acute pancreatitis	32	86
Other	5	14
If pancreatitis, causation		
Alcohol	11	34
Gallstones	9	28
Other	12	38
Metoclopramide prior to insertion		
Yes	37	100
No	0	0
Patient able to assist		
Yes	25	68
No	12	32
Patient able to take sips of water		
Yes	25	68
No	12	32
Inserted by		
Senior dietitian	13	35
Clinical nurse specialist	20	54
Other	4	11
Proceeded to radiological confirmation		
Yes	35	95
No	2	5
Correct position (*n* = 35)		
Yes	32	91
No	3	9

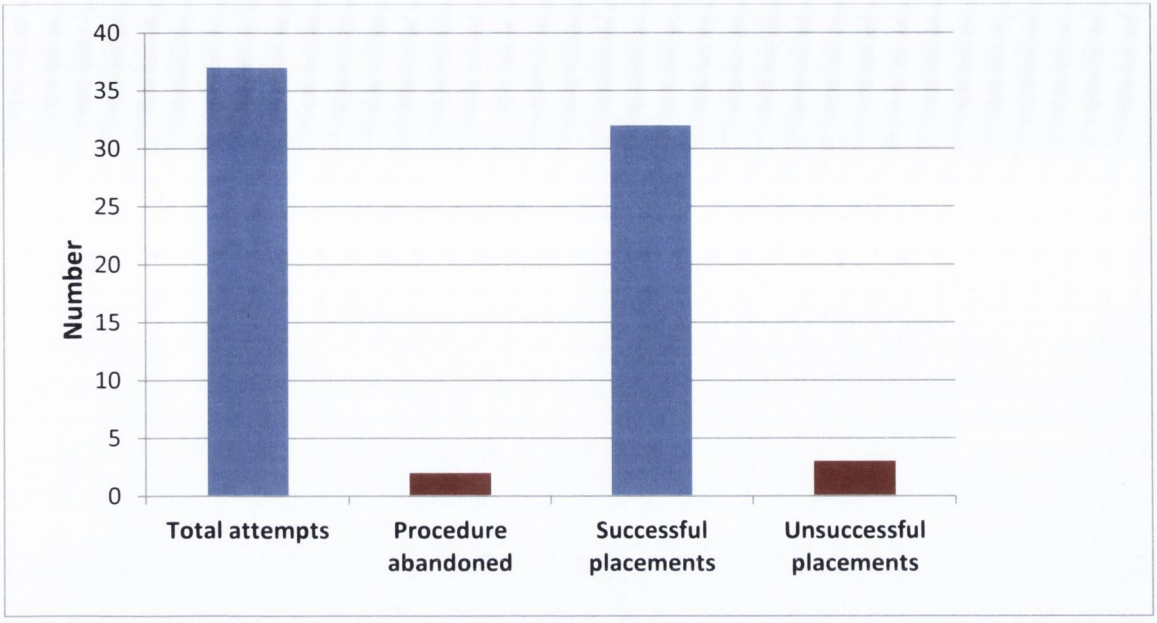


Figure 5.4 Total attempts and success rates of blind bedside tube insertion

Table 5.2 Comparison of estimated costs for bedside versus endoscopic insertion

	Euro
Estimated cost of bedside insertion	
NJ tube	12.90
lubricant gel	0.50
Dressing pack	0.74
50ml syringe	2.85
10ml syringe	1.50
PFA	50.00
Clinical nurse specialist / senior dietitian 30 minutes (mean)	14.10
Porter 30 min	7.91
Total bedside	**90.50**
Estimated cost of endoscopic insertion	
NJ tube	12.90
lubricant gel	0.50
Dressing pack	0.74
Endoscopy procedure	250.00
Endoscopist 30 minutes	47.16
Staff nurse 30 minutes x3	32.34
Porter 30minutes	7.91
Total endoscopy	**351.55**

5.2.3 Discussion

5.2.3.1 Results compared to the literature

This study demonstrated that the 10,10,10 procedure is a safe, simple and cost-effective technique for small bowel tube insertion, with a success rate for small bowel placement of 86.5%. This is the first unit in Ireland, and among the first in the UK, to undertake this initiative and the success rate of the present study compares favourably with other studies describing a variety of insertion techniques. Previously reported success rates have been variable: 78% (electromegnetic-guided tube placement)[135]; 83-95% (blind bedside placement)[136-137]; 84.2% (fluoroscopic insertion in the intensive care unit, ICU)[138]; 88% (air insufflation and electrocardiographic (ECG) monitoring)[139]; 88-95% (magnetically-guided feeding tube)[140-141].

The time taken for tube insertion in this study (mean time 33 minutes for preparation and insertion) did not differ greatly from mean times described in a number of comparable studies: 28 minutes[142], 30 minutes[136] and 60 minutes[143]. Times for alternative methods were 40 minutes (mean time, electromagnetic method)[135], 17 minutes (median time, fluoroscopy method)[138] and 15 minutes (median time, electrocardiogram (ECG) monitoring)[139]. No adverse events following or during tube insertion were observed, outside of the two incidences where the tube insertions were abandoned early in the procedure. One other study noted a few adverse events (1 nosebleed, 1 atrial fibrillation, 2 desaturation episodes). Other studies reported no adverse events or acute complications[135, 138], including studies which described blind insertion techniques similar to the current technique[133, 142-143]. Satisfaction with the procedure method amongst staff or patients was not measured in the current study. One study that surveyed nurses and physicians following the implementation of a dietitian-led blind placement protocol reported a 100% satisfaction rate for the blind placement compared to the previously-utilised methods[134].

5.2.3.2 Alternative methods of NJ tube insertion

The 'air-insufflation' technique involves injecting a large volume of air into the stomach to distend the stomach and facilitate feeding tube passage through the pyloric sphincter.

Following the confirmation of gastric tube position, a bolus of air (volume varies between studies) is injected into the stomach in a single bolus. The tube is then advanced in small increments with an additional small air bolus (10ml) after each advancement, while simultaneously auscultating over the abdomen to ascertain the tube's location. When auscultation is heard predominantly over the right upper quadrant, transpyloric passage is deemed probable and radiological confirmation is sought[144]. Varying degrees of success have been reported, from 66% (increasing to 77% on repeat radiograph)[145], to 83%[136] and 88%[146]. Slagt and colleagues[139] described an 88% success rate with a method of tube insertion that involved the administration of erythromycin intravenously, followed 30 minutes later by gastric tube placement and the insufflation of 5-10ml/kg air into the stomach. Continuous ECG guidance was done to monitor for a change in polarity of the QRS complex, suggesting that the tip of the tube had crossed the midline and therefore transpyloric passage of the tube. Exact tube position was confirmed by radiograph. Electromagnetically visualised placement methods (such as the *Cortrak*® machine) utilises computer technology to allow the guided (non-blind) bedside insertion of naso-jejunal tubes. Clinicians are guided in the placement of tubes into the gut by showing the relative location of the feeding tube tip which is an electromagnetic transmitter. A receiver unit is placed at the patient's xiphoid process and acquires a signal from the stylet as it moves during the procedure. Benefits of this method are that an additional radiograph is not required, and that the risk of permanent tube placement into the airways is minimised as clinicians are able to respond in real time to modify the path of the tube as required. In a study on ICU and burns patients who were randomised to either the *Cortrak*® method or bedside endoscopy, there were no differences in success rates between the two techniques (both greater than 90% success)[147]. Gabriel *et al* described a further technique for the placement of tubes in the distal small bowel in which the tube contains a small magnet at its distal end and a magnetic field sensor. A handheld external magnet is used over the abdomen to manoeuvre and steer the tube tip through the pyloric sphincter into the duodenum (magnetically-guided feeding tube). In several studies, the innovators of the technique described success rates of 88-95%[140-141, 148].

5.2.3.3 A potential expansion of the role of the dietitian

This study investigated the feasibility and safety of blind bedside tube insertion by nurses and dietitians. While nursing staff already participate in NG tube insertion, this study (and others) builds on prior research which highlighted a significant potential extension of the current role of the dietitian. Success rates tend to vary between staff types and grades in different studies. Zaloga[149] reported a high success rate (92%) with a doctor-led blind tube insertion technique, but this decreased to 70-80% when less experienced house staff placed the tubes. By having dedicated, trained clinicians placing feeding tubes success rates may be improved. Nurses and dietitians employed permanently may be well-placed to take on this role as there is potential for this skill to be lost from the original institutions as doctors move from hospitals during training. Cresci *et al*[142] described high success with a dietitian-led insertion protocol (95% success), while a high success rate was similarly described with the use of a dietitian/nurse team approach (86%)[134]. Table 5.3 summarises the studies to date investigating the role of dietitians and nurses in the placement of bedside tube insertion.

5.2.3.4 Study limitations

- The study was not controlled (the new technique was not directly compared to the local traditional insertion methods), instead, a review of the practice change was undertaken
- The time of preparation and insertion was recorded, but not the time of waiting, undertaking and reading a PFA for position confirmation, therefore the improvements in time may not be an accurate representation if the PFA (or reading of the PFA) is delayed
- An improvement in timeliness of the bedside insertion compared to the endoscopic / radiological placement was postulated, however, the time of the traditional methods prior to the bedside insertion was not measured
- Patient and staff satisfaction with the new technique was not measured

5.2.3.5 Study strengths

- This is the first study of this type in Ireland and among the first in the UK representing the introduction of a novel technique. To date, the majority of studies in this area have been undertaken in the US.
- This study demonstrated the potential for the extended role of the dietitian and nurse
- Success rates in the present study were comparable to other similar studies on bedside NJ insertion, and to studies of other NJ insertion techniques

Table 5.3 Studies reporting tube insertions by dietitians and dietitian/nurse teams

	Method	Numbers	Results	Comments
Duggan *et al*, (Current study) Ireland	**Bedside 10,10,10 protocol**	**Dietitian placed 13 tubes; nurse placed 20 tubes; 37 total tubes placed**	**86.5% placed post-pylorically**	**Decrease in costs by 75%**
Meyer *et al* [137], 2007 UK	Bedside; protocol-led placement	Nurse/dietitian: 194 tubes placed over 2 years (paediatric)	94.4-95% success	Well-monitored education programme, regular auditing, team support
Gray *et al*[135], 2007 USA	ETPD compared to blind placement by ICU nurse	Dietitian/nurse team placed 81 tubes	78% success; 50% decrease in x-rays using ETPD *vs* blind insertion	Decrease in x-ray costs; more timely insertions
Jimenez *et al*[143], 2004 USA	Bedside (based on Cresci *et al*, 2003)	Dietitian placed 18 tubes	85% placed post-pylorically	Fewer EN feeding interruptions and less PN
Cresci *et al*[142], 2003 USA	Bedside; protocol-led placement	Dietitian placed 135 tubes	95% placed post-pylorically	Timely, cost-effective; protocol easily taught
Taylor *et al* [134], 2001 USA	Bedside; protocol-led placement	Dietitian placed 36 tubes ; nurse placed 38 tubes	86.4% placed post-pylorically	Improved rates with protocol

ETPD, electromagnetic tube placement device

5.3 Part 2: A three-year audit of nutrition support in acute pancreatitis

5.3.1 Methods

5.3.1.1 Setting and data collection

A period of three years (January 2006 to December 2008) was selected for review. Our institution received 397 pancreatitis admissions over that period, of which 354 had acute pancreatitis. Consecutive patients (n = 62, 17.5%) who required nutrition support were included; the remainder of patients were deemed not to require specialised feeding. Patient details were routinely loaded onto clinical and nutritional databases. Additional information was obtained *via* an electronic patient coding system. Medical and nutritional records were used to further elucidate clinical data, and to validate the datasets. The following data were recorded: demographics; aetiology; modified Imrie score (measured at admission where patients presented to the institution, and reconstructed when tertiary referrals, see Chapter 4); CRP (mg/L, on admission and on the day of feeding commencement); BMI (stratified according to the WHO classification, see Chapter 4); 'days to enteral feeding' (day feeding started post admission); EN/PN; gastric/jejunal feeding route; duration of feeding; complications; surgical intervention; ICU transfer; mortality, and LOS.

5.3.1.2 Nutritional intervention

Patients requiring nutrition support were referred to the Clinical Nutrition & Dietetics service. The decision to feed was made based on clinical evaluation (pain, symptoms), disease severity and/or a raised CRP (>150 mg/L). Feeding was commenced according to the departmental feeding algorithm which gave emphasis to the enteral route of feeding (see Figure 5.5). As described in Part 1 of this Chapter, bedside NJ insertion was introduced during the study period to facilitate the timely placement of feeding tubes and thus early feeding. Patients receiving nutrition support were monitored daily by the pancreatico-biliary or ICU dietitians and the nutritional care plan was adjusted according to tolerance and requirements. PN was commenced if EN was not feasible or not tolerated.

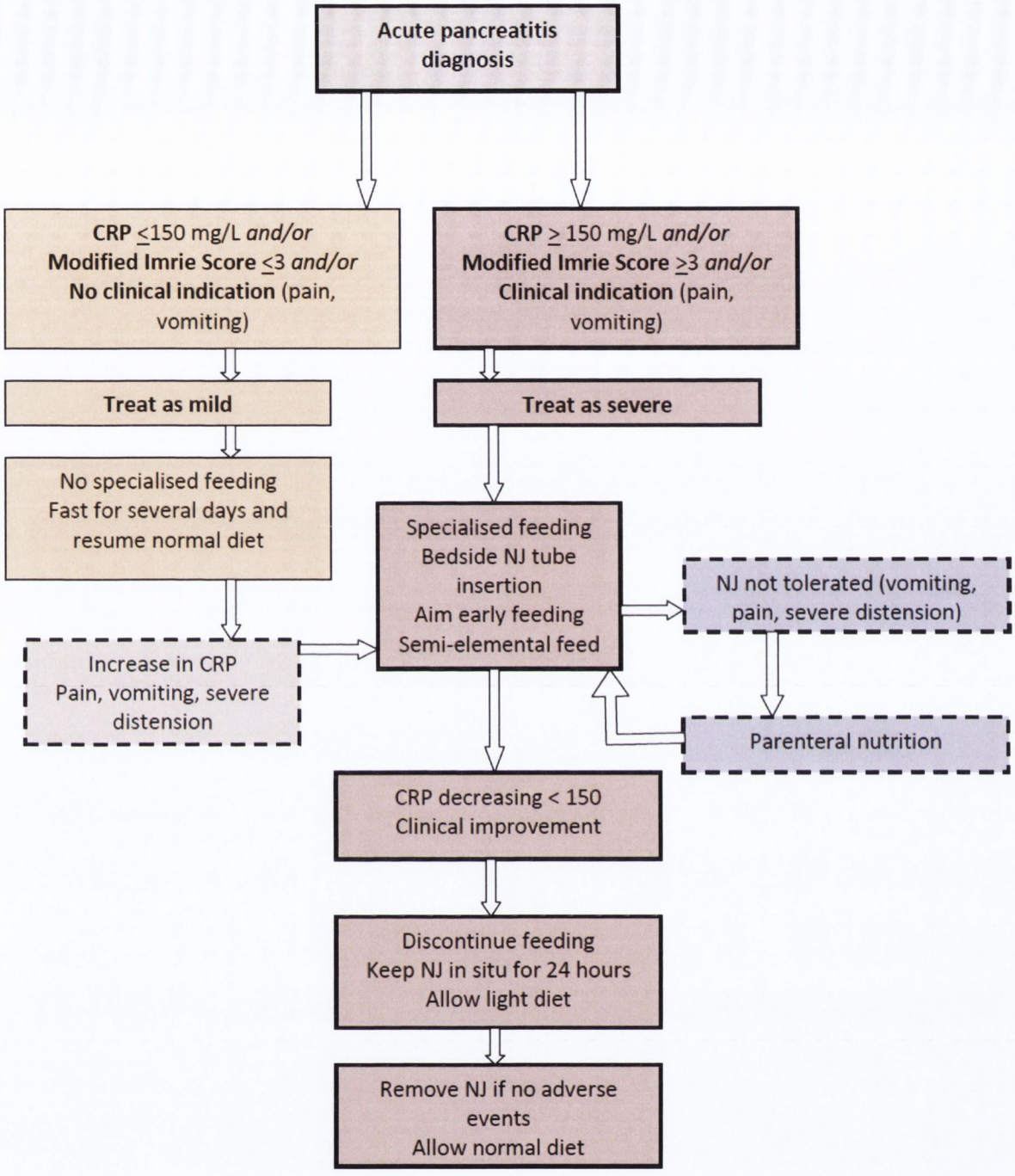


Figure 5.5 Tallaght Hospital Centre for Pancreatico-Biliary Disease acute pancreatitis feeding protocol 2006-08

5.3.1.3 Audit standards

Nutrition-related recommendations from international guidelines are listed below, and are supported by a single-study reference in areas of ambiguity or controversy. These nutrition-related guidelines were identified as key standards against which local nutritional practice may be measured.

- EN recommended over PN as first line nutritional treatment[18, 26, 55-56, 78-79]
- PN not first line, however supplementary PN may be given where EN not possible[55]
- The route of EN may be NG or NJ[78], but the jejunal route may be better tolerated if gastric not tolerated[56]. Jejunal feeding results in reduced pancreatic stimulation[78]
- Standard enteral formula may be used if tolerated[56], but the provision of peptide-based, MCT-based or fat free formulae may help improve tolerance[78]. Peptide feeds are known to be safe[56].
- It is recommended that patients are fed early [55-56, 78], however, no definite timeline for starting is recommended. Some studies recommended starting feeding within 2 days (48 hours) of feeding[76]
- Aetiology should be determined in at least 80% of cases, and no more than 20% should be classed as idiopathic[18]
- All patients with severe acute pancreatitis should be managed in ICU[18]
- Mortality should be less than 10% overall[18], and less than 30% in severe (complicated) disease[18]

5.3.1.4 Statistical analyses

The study design was a retrospective review of a prospectively held database. Data were analysed using Minitab Release 15 (Minitab inc., USA). Chi-squared (χ^2) analysis was used to analyse categorical data. Where mean is given, SD is given in parentheses. In all cases, a *P* value of <0.05 was considered statistically significant.

5.3.2 Results

5.3.2.1 Patients

Of 397 patients with pancreatitis admitted to the unit, 354 were diagnosed with acute pancreatitis. Sixty-two patients received nutrition support and were included in the analysis. The majority of patients were male (n = 49, 79%). Aetiology was known in 51 of 62 patients, and the major aetiological factors (where known) were alcohol or gallstones (82.3%). The mean (SD) age was 48.7(15.4) years, the median age was 47.9 years, and the age-range was 20.5 – 86.5 years. BMI was known in 46 of 62 patients; the mean (SD) BMI was 28.7(5.6) Kg/M^2, the median was 28.4, and the BMI-range was 19.5 – 40.9 Kg/M^2. Table 5.4 summarises patient characteristics.

5.3.2.2 Nutrition support practices

More than 9 in 10 patients were commenced on EN (93.5%) rather than PN. Of those, the majority were fed *via* an NJ tube (n = 57, 91.9%) and one patient *via* an NG tube. All patients receiving EN were fed with a semi-elemental (peptide-based) formula. Most patients (69.4%) received *only* EN during the course of their disease, for a mean (SD) duration of 11.3 (9.8) days. However, 24.1% (n = 14) of patients who were started on EN required supplemental PN. Where PN was delivered, the mean (SD) duration was 12.6 (12.3) days. Feeding details are summarised in Table 5.5.

	n	%
Sex		
Male	49	79.0
Female	13	21.0
Age (years)		
18-34	10	16.1
35-54	32	51.6
55-74	17	27.4
>75	3	4.8
Aetiology[α]		
Alcohol	31	60.8
Gallstones	10	19.6
ERCP	6	11.8
Idiopathic	3	5.9
Hypertriglyceridemia	1	1.9
BMI (Kg/M^2)[#]		
Underweight, BMI <18.5	0	0
Normal weight, BMI 18.6-24.9	12	26.1
Overweight, BMI 25.0-29.9	19	44.2
Obese, BMI >30.0	15	32.6

Table 5.4 Characteristics of patients with acute pancreatitis who received nutrition support

α Aetiology known for *n* = 51 patients, # BMI known for *n* = 46 patients

		n	%
Disease severity (Imrie score)			
Mild or moderate		45	72.6
Severe		17	27.4
	Imrie score 3	9	
	Imrie score 4	7	
	Imrie score 5	0	
	Imrie score 6	1	
Feeding practices[#]			
Enteral Nutrition	Started on EN	58	93.5
	Jejunal route (NJ)	57	91.9
	Gastric route (NG)	1	1.6
	Received EN only	43	69.4
Parenteral Nutrition	Started on PN	3	4.8
	Required PN supplementary to EN	15	25.9
Reasons for PN	Tube dislodgements/insertion difficulties	7	
	Intolerance to EN	4	
	Physiological contraindications	3	
	Started out of hours	2	
	Started in other hospital	1	
	Unknown	1	

Table 5.5 Disease severity and feeding details for patients with acute pancreatitis

#Data for $n = 61$

5.3.2.3 Days to enteral feeding

The mean (SD) 'days to enteral feeding' was 4.1 (2.5), with a median of 4 days. The blind bedside NJ insertion initiative described in Part 1 was undertaken during the three year review period. There was a greater delay in starting feeding before the NJ insertion project (5.4(2.3) days) than after (mean 3.5 (2.5) days) (P = 0.014).

5.3.2.4 Disease severity

Based on the modified Imrie score, three-quarters of the group had predicted mild/moderate disease (n = 45, 72.6%), and 27.4% (n=17) had predicted severe disease (see Table 4.6). The mean CRP on the day of feeding commencement was 250.8 (121.3) mg/L, with a range of 1 – 494.1 mg/L. Eleven of 17 patients who had predicted severe disease were transferred to ICU during their inpatient stay.

5.3.2.5 Mortality

Two patients died in the 3-year period; representing 3.2% of the fed group and 0.6% of total acute pancreatitis admissions. Both non-survivors were male, with a mean (SD) age of 67.8(3.79) years. Non-survivors were significantly older than survivors (P = 0.022; CI (-36.1, -7.55)). There was no significant difference in the CRP on admission (P = 0.126), or in the day of feeding initiation (P = 0.768) between those who survived or not. Both non-survivors had predicted severe disease, with high modified Imrie scores (4 and 6). Both non-survivors required ICU transfer, PN feeding and suffered multi-organ dysfunction, renal dysfunction and required drainage procedure(s).

5.3.2.6 Complications

Forty-five percent (n = 25) of the group had at least one complication. Twelve patients (19.3%) had pancreatic sepsis, and 13 patients (21%) had renal dysfunction or failure (of which 8 patients required dialysis). No patient required surgical intervention, although 8 patients required drainage procedures. The incidence of complications, requirement for surgery/drainage and mortality was examined according to predicted severity of disease (see

Table 5.6). There were statistically more pancreatic sepsis ($P < 0.001$), renal dysfunction ($P < 0.01$), requirement for renal dialysis ($P = 0.024$), and 'any' complication ($P = 0.004$) in those predicted severe, than in those predicted mild or moderate. There were a statistically higher requirement for drainage procedures among those predicted severe than those predicted mild or moderate. Those with predicted severe disease were more likely to require PN ($P = 0.038$). Due to small clinical event numbers ($n = 2$), mortality was not amenable to χ^2analysis.

5.3.2.7 Practice compared to standards

Table 5.7 details local practice over the study period according to predefined standards. Mortality was further compared against Irish national mortality data for acute pancreatitis during the same period, provided by the Economic and Social Research Institute (ESRI) *via* the Hospital In-Patient Enquiry (HIPE) system, Tallaght Hospital (personal communication)[150].

Table 5.6 Analysis of occurrence of complications, interventions and mortality according to disease severity

		Predicted mild / moderate Imrie score ≤2		Predicted severe Imrie score ≥3		*P*
		n	%	n	%	
Any complication	**Yes**	12	21.8	13	23.6	
	No	27	49.1	3	5.5	0.004*
Pancreatic sepsis	**Yes**	3	5.6	8	14.8	
	No	35	64.8	8	14.8	0.000*
Renal dysfunction	**Yes**	4	7.3	9	16.4	
	No	35	63.6	7	12.7	0.00*
Renal dysfunction requiring dialysis	**Yes**	3	5.4	5	9.1	
	No	36	65.5	11	20.0	0.024*
Surgical intervention	**Yes**	0		0		
	No	37	71.2	15	28.8	#
Drainage procedure	**Yes**	1	1.9	7	13.2	
	No	37	69.8	8	15.1	0.000*
Required PN	**Yes**	9	14.8	8	13.1	
	No	35	57.3	9	14.8	0.038*
Death	**Yes**	0		2	3.2	
	No	45	72.6	15	24.2	#

* Statistically significant difference at $P < 0.05$, # Pearson's χ^2 test invalid due to small numbers

Table 5.7 A comparison of local clinical and nutritional practice in acute pancreatitis compared to international standards

	International standards	Study findings
EN usage	- EN recommended over PN as first line nutritional treatment	- 93.5% started on EN
PN usage	- Not first line - Supplementary PN may be given where EN not possible	- 4.8% started on PN -25.9% of EN group required supplementary PN
EN route	- NG or NJ -Jejunal route if gastric not tolerated - Jejunal feeding results in reduced pancreatic stimulation	- 91.9% NJ
EN formula	-Standard formula if tolerated -Peptide-based, MCT-based or fat-free formula might improve tolerance	-100% fed with peptide-based formula
Timing of feeding	- Early feeding - No definite timeline recommended - Within 2 days (48 hours) in some studies	- Overall mean delay in starting feeding: 4.1 days - Improved from mean 5.4 to 3.5 days following introduction of blind bedside insertion (see Part 1 of this Chapter)
Aetiology	- Aetiology should be determined in at least 80% of cases, no more than 20% idiopathic	- Idiopathic classification in 4.8% - 'Unknown' classification in 17.7% (missing data)
ICU for severe cases	-All patients with severe acute pancreatitis to be managed in ICU	-65% treated in ICU (11 of 17 patients with Imrie score $\geq$3)
Mortality	- <10% overall - <30% severe (complicated) disease - Irish national mortality for acute pancreatitis inpatients 3.3%	- 0.54% overall - 8%: any complication (n = 25): - Among fed group (n = 62): 3.2%

5.3.3 Discussion

This study examined management of patients with severe acute pancreatitis regarding nutrition support, mortality, severity, complications and compliance to international standards.

5.3.3.1. Nutritional management

EN (rather than PN) has been unanimously recommended by nutritional management guidelines for acute pancreatitis. In the present study, more than 9 in 10 patients were started on EN rather than PN, representing an adoption of the enteral route of feeding in this institution. The ideal enteral route (gastric or jejunal) is less clear-cut, with both NG and NJ being recommended[18, 78]. Therefore in practice the enteral route is a matter of clinical preference for the individual teams, as well as being dependant on the clinical status of individual patients. In this audit, for the vast majority of patients feeding was provided *via* the jejunal route. Despite an arguably more conservative feeding approach (jejunal rather than gastric feeding, peptide-based feeds rather than standard formula), a quarter of patients still required supplementary PN. Reasons for PN included difficulties with tube insertion or dislodgement, intolerance to EN, or physiological contraindications. The achievement of early feeding, which is recommended by three of the major nutritional guidelines, was more elusive. Nevertheless, there was a notable improvement in the timely commencement of feeding during the study period following the introduction of bedside NJ insertion. Results of the present study compare favourably with previous similar studies. In an audit of acute pancreatitis management in two UK hospitals (a district general hospital and a teaching hospital), only six patients were reportedly fed at all, and only two solely with enteral feeding[151]. However, this study which was published in 2001 reported on data that was 4-5 years old at that time. Since the earliest nutritional guidelines for acute pancreatitis were not published until 2002[55], the failure to feed may be reflective of a lack of research and guidelines for nutrition at that time. To illustrate the tidal shift in practice regarding nutrition in pancreatitis in the last 10-15 years, a study from India published in 2012 on 50 patients with severe acute pancreatitis reported that all 50 patients received EN (a mix of NG, NJ and feeding jejunostomy)[152]. However, success with EN was not absolute in this

study. Only 14% of patients received EN only, and 80% received EN with supplementary PN. In what may be a reflection of the severity of pancreatitis in that group, the mortality was notably high (60%).

5.3.3.2 Clinical outcomes

At 0.54%, the overall mortality for acute pancreatitis admissions (including mild, moderate and severe severity grades) is well below international levels. For the study group (n = 62), the mortality rate was 3.2%, and for those with 'complicated disease' the mortality rate was 8%. The UK working party on acute pancreatitis standards (2005) stated that mortality should not exceed 10% overall, or 30% in severe (complicated) disease[18]. Mortality in our group also compared favourably with national Irish data provided by the Economic Social and Research Institute (ESRI) which showed national acute pancreatitis mortality for the same period at 3.3%. Compared to other published acute pancreatitis audits of practice, mortality in the present study also compares well. Mofidi and colleagues published a mortality rate of 5.9% in 759 acute pancreatitis patients, and 19.6% in severe acute pancreatitis[153]. Dube *et al* reported a mortality of 4.2% in all acute pancreatitis patients and 26.7% in severe patients in a UK teaching hospital[151]. In another UK audit of 8 hospitals in a single geographic area, Toh *et al* reported a mortality of 9.1% in all acute pancreatitis patients and 28% in severe acute pancreatitis[154]. The UK guidelines specify that all patients with severe acute pancreatitis should be managed in a high dependency or ICU with full monitoring and systems support[18]. Only two thirds of the patients in the present study were managed in ICU (for part of their hospital stay). However, both patients that died received ICU care. Some patients with severe disease were not transferred to ICU but there were no deaths among this group.

5.3.3.3 Aetiology

The UK guidelines[18] stated that no more than a fifth of patients should be classified as idiopathic, and that determination of cause should include a vigorous search for gallstones, use of endoscopic ultrasound, bile sampling, fasting blood lipids, calcium, viral antibody titres, and consideration of underlying neoplasm or chronic pancreatitis[18]. In the present

study, idiopathic classification was low at 4.8%; however a high proportion of patients were recorded as 'unknown', which may be representative of additional 'idiopathic' diagnoses, or may be indicative of a system failure in data recording.

5.3.3.4 Disease severity

Patients were stratified for severity according to the Imrie classification, the data show that those with predicted 'severe' disease were statistically more likely to have 'any complication', or any individual complication, and to require a drainage procedure. The two patients who did not survive had predicted 'severe' disease. Similarly, those with predicted severe disease were more likely to require PN. Therefore, these data indicated that the Imrie score was useful in predicting complications and mortality. Nevertheless, some patients with predicted mild or moderate disease also suffered complications, and nine required PN - indicating problems with gut access or intolerance to EN.

5.3.3.5 Study limitations

This represents the first Irish study comparing practice in acute pancreatitis to published guidelines

- This study had a small sample size and presented data from a single institution
- Data on the percentage feed received *versus* feed prescribed was not recorded, therefore some patients may have received very little of prescribed feed which could impact outcomes
- The study included selected audit parameters from the UK guidelines along with parameters from the main nutrition in acute pancreatitis guidelines. Other recommended audit measures from the UK guidelines were not within the scope of this project
- When comparing outcomes such as mortality to those of other studies, methodological and sampling differences must be taken into consideration which could partially explain the varied outcomes. The relatively low mortality in the present study could arguably be due to a less severe patient group

5.3.3.6 Study strengths

- Despite low sample size, statistically significant differences were found
- The audit highlighted deficiencies in clinical practice which allows improvement in patient care. Areas highlighted included the transfer of severe acute pancreatitis to a high dependency unit or ICU, and improvements in determination of disease aetiology and database loading

5.4 Part 3: An international study of nutritional practice in acute pancreatitis

5.4.1 Methods

5.4.1.1 Survey

Study design was a cross-sectional survey of the nutritional management of acute pancreatitis patients across six countries. An 8-section, 37-item survey was designed for completion by dietitians (Appendix G). Replies were anonymous, although respondents were invited to leave a contact email. Internet protocol (IP) addresses were recorded. The survey was piloted on dietitians within Tallaght Hospital who were not eligible to participate in the survey. Following this, the survey questions and layout were further refined. The survey sections were comprised of the following:

Section 1: Dietitian contact with acute pancreatitis

Those who responded 'no' were directed to the survey end and excluded

Section 2: Setting (institution type, beds, dedicated pancreatitis team)

Section 3: Feeding practice

Section 4: Tube insertion

Section 5: Additions to regimens

Section 6: Discontinuing feeding

Section 7: Guidelines

Section 8: Demographics

5.4.1.2 Data collection

The survey was distributed by email or webpage to dietitians in the UK (including England, Scotland, Wales and Northern Ireland), the Republic of Ireland, and Canada. In the UK and the Republic of Ireland, the survey was distributed *via* the Nutrition Interest group of the Pancreatic Society of Great Britain and Ireland (a working group of dietitians from Ireland and the UK who manage patients with pancreatic disease). In Ireland, the survey was further distributed *via* the Dietetics professional body: the Irish Nutrition & Dietetic Institute (INDI). In the UK, the survey was placed on the UK Dietetics professional body: the British Dietetic

Association (BDA) member's only website, and distributed *via* electronic publication *E-Zine*. In Scotland, surveys were also distributed *via* the Scottish Intensive Care Society Dietitian's group. In Canada, the survey was distributed by email using professional contact lists throughout seven Canadian provinces, coordinated by a dietitian located in British Columbia.

5.4.1.3 Determination of response rate

- Determination of the survey response rate was not possible for several reasons:
- The number of dietitians working in acute pancreatitis in each country was not known
- Members of the Nutrition Interest group of the Pancreatic Society of Great Britain and Ireland were initially targeted (n = 44), however, to ascertain practice in smaller institutions; the survey was extended to non-members
- In some institutions, several dietitians may have a role in the nutritional management of acute pancreatitis
- As this was a survey of dietetic practice, the survey was not limited to 1 per institution
- Due to the electronic nature of the survey distribution, it was not possible to ascertain the number of times the survey was forwarded by email

5.4.1.4 Comparison to guidelines

To compare practice to guidelines, seven acute pancreatitis management parameters were set out based on the six commonly used acute pancreatitis guidelines (Table 5.8).

5.4.1.5 Ethical considerations

Ethical approval was awarded by the chairman of the Joint Ethics Committee of St. James and Tallaght Hospital.

5.4.1.6 Data analyses

Analyses were conducted using Minitab 15 (Minitab Inc. US). χ^2 analyses were performed to examine the differences in categorical variables. A *P* value of <0.5 was considered significant.

Table 5.8 Seven parameters used to benchmark practice against the six main pancreatitis nutrition guidelines

Parameter 1	Every hospital receiving acute admissions should have a single nominated clinical team to manage all patients with acute pancreatitis (E) Specialists in nutrition should form part of the multidisciplinary team in specialist units for the treatment of severe acute pancreatitis (E)
Parameter 2	Early feeding for patients with severe acute pancreatitis is recommended (A, B, D)
Parameter 3	EN is preferred over PN (A, B, C, D, E, F)
Parameter 4	Jejunal feeding could be trialled if gastric feeding is not tolerated (B); either gastric or jejunal feeding may be used, but tolerance may be increased by a tube placed lower in the gut (D); The NG route can be used as it appears to be effective in 80% of cases(E); NJ feeding is preferred (over PN) (F)
Parameter 5	Indirect calorimetry is the most ideal method of calculating requirements (D); the Harris Benedict equation is unreliable where there are septic complications (A); 25-35 kcal/Kg/day for severe acute pancreatitis, low caloric provision (15-20 kcal/Kg/day) during the early catabolic stages of complicated disease (A)
Parameter 6	Peptide-based feeds are known to be safe, but standard feeds could be tried it tolerated (B); Tolerance may be improved by altering the formula type, including trying a peptide-based feed (D)
Parameter 7	Glutamine should be administered with PN (C)
Guidelines	
ESPEN guidelines on nutrition in acute pancreatitis[55]	
ESPEN Guidelines on Enteral Nutrition: Pancreas[56]	
ESPEN Guidelines on Parenteral Nutrition: pancreas[79]	
ASPEN Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient [78]	
UK guidelines for the management of acute pancreatitis. UK Working Party on Acute Pancreatitis[26]	
Practice guidelines in acute pancreatitis. American College of Gastroenterology[17]	

5.4.2 Results

5.4.2.1 Demographics and settings

In all, 253 dietitians took the survey. Forty-nine dietitians who did not work in acute pancreatitis were excluded. Therefore, 204 were included in the final analyses. For reporting of results, the Republic of Ireland is referred to as 'Ireland', and England, Scotland, Wales, Northern Ireland are amalgamated as 'UK'. Response per country was Ireland, *n* = 31, UK, *n* = 56, Canada, *n* = 117. Based on data from the respective professional bodies, this represented an estimated 6.2%, 0.9% and 2% of registered dietitians in each country respectively. The majority of responders were employed in district or general hospitals, and a third (38.7%) were employed in university hospitals. Within Canada, 34 (29%) were university hospital dietitians compared to 45.2% (*n* = 14) in Ireland and 55.3% (*n* = 31) in the UK. The UK had the greatest response from larger hospitals, with over half (53.6%) reportedly working in a hospital with >600 beds, compared to 25.8% in Ireland and 18.9% in Canada (Table 5.9).

5.4.2.2 Caseloads and specialist teams

Dietitians were asked to estimate the percentage of clinical caseload allocated to pancreatic disease. Sixteen percent (*n* = 9) of UK responders reported a caseload of greater than 30%. Among Irish responders, 6.7% (*n* = 2) reported a greater than 30% caseload, as did one dietitian in Canada. One dietitian in Ireland and three in the UK reported a pancreatic caseload of greater than 50%. Over half of responders in Ireland (51.6%, *n* = 16) and Canada (57.3%, *n* = 67) were qualified for greater than 8 years, compared to 37.5% (*n* = 21) in the UK. More than a third reported acceptance of tertiary pancreatic referrals (Table 5.9). Almost one-quarter of UK dietitians (23.2%, *n* = 13) reported the existence of pancreatic multidisciplinary team at their institution, less than ten percent of Irish and Canadian dietitians reporting the same thing. Regarding whether or not their teams had a formal pancreatitis management protocol, 21.4% (*n* = 12) of responders in the UK, 8.3% (*n* = 3) of Irish and 5.1% (*n* = 6) of Canadian responders reported that such a protocol existed. Dietitians were further asked about the existence of a formal pancreatitis *feeding* protocol; 16.6% (*n* = 9) in the UK, 6.0% (n = 7) in Canada and 5.5% (n = 2) in Ireland reported the

presence of such a protocol (Figure 5.6). Using χ^2 analysis, units that accepted tertiary referrals were more likely to have a pancreatic multidisciplinary team ($P < 0.0001$), and a formal *feeding* protocol ($P = 0.041$), but not a formal pancreatitis management protocol ($P = 0.363$).

Table 5.9 Demographics and management-pattern of respondents compared by country

	Ireland n	UK n	Canada n	Total
Completed surveys	31	56	117	204
Sees acute pancreatitis patients regularly	17	42	86	145
See acute pancreatitis patients occasionally	14	14	31	59
Age *<25 years*	3	7	4	14
26- 33 years	15	30	39	84
34 -42 years	6	11	32	49
43- 51 years	4	6	18	28
>52 years	1	1	22	24
Male	1	6	4	11
Female	28	49	111	188
Years qualified *0- 3 years*	3	15	21	39
4- 8 years	10	19	26	55
> 8 years	16	21	67	104
University hospital	14	31	34	79
District/ general hospital	16	25	78	119
Private hospital	1	0	0	1
Other	0	0	5	5
0-200 beds	8	0	33	41
201-400 beds	10	11	38	59
401-600 beds	5	15	24	44
601-800 beds	7	8	11	26
> 800 beds	1	22	11	34
Pancreatic disease caseload				
0- 5%	15	26	76	117
6- 10%	12	9	29	50
11-30%	1	12	8	21
31- 50%	1	6	0	7
51-100%	1	3	0	4
Accept tertiary referrals?				
Yes	12	27	39	78
No	12	12	29	53
Unsure	7	17	47	71
Pancreatic multi-disciplinary team present?				
Yes	3	13	4	20
No	28	40	109	177
Unsure	0	2	2	4
Patients with severe acute pancreatitis transferred to ICU or HDU?	15	27	37	79
Yes	14	11	58	83
No	1	18	21	40
Unsure				
Formal pancreatitis management protocol?				
Yes	3	12	6	21
No	24	18	91	133
Unsure	4	26	20	50
Formal pancreatitis feeding protocol?				
Yes	2	9	7	18
No	28	43	108	179
Unsure	1	4	2	7

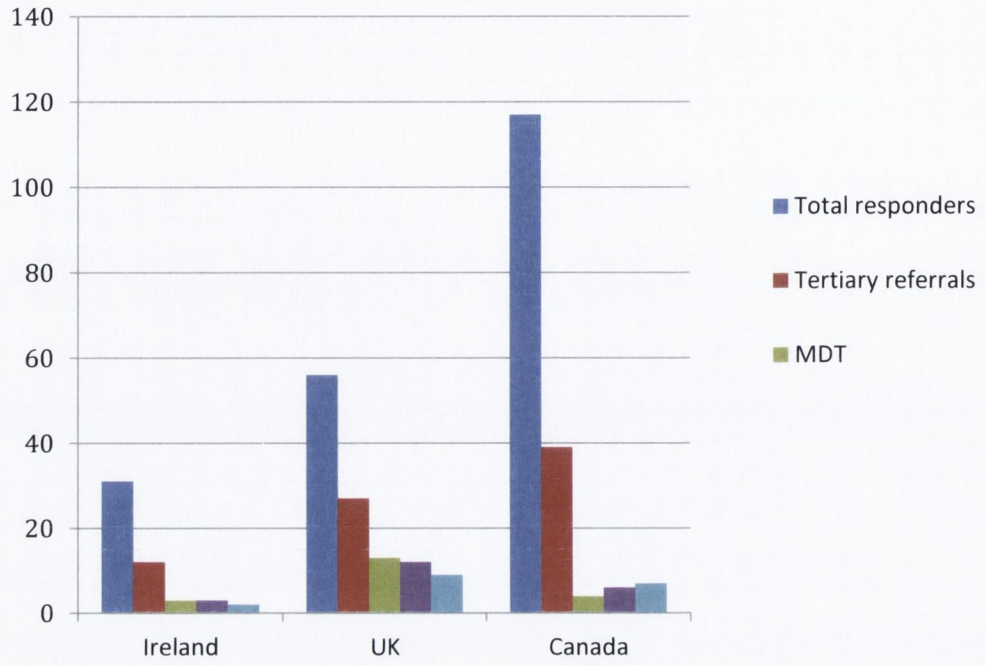


Figure 5.6 Total survey respondents and breakdown regarding the existence of teams and management protocols, per country

5.4.2.3 Feeding commencement

Respondents were asked to state what they considered *'early feeding'* to be from a given range of between <12 and <72 hours. The most common response was '<24 hours' (50.8%). A minority (5.2%) considered <12 hours to be *'early feeding'*. Most (92.8%) chose 48 hours or less as *'early feeding'*. For the survey, dietitians were provided with 3 clinical scenarios for which they were asked to state their practice in terms of timing of feeding. The clinical scenarios were as follows:

1) Severe acute pancreatitis

2) Severe acute pancreatitis with obese-range BMI

3) Severe acute pancreatitis with pre-existing malnutrition

More than half (54.2%) reported that they would feed early in severe acute pancreatitis, with less (42%) reporting that they would feed early in the case of an obese patient, and 81.9% would feed early where there is pre-existing malnutrition. The data was further analysed per institution-type using χ^2 analysis. Respondents were more likely to feed earlier in university hospitals compared to district/ general hospitals in severe acute pancreatitis (P = 0.015). Similarly those working in university hospital were more likely to feed early in the obese acute pancreatitis patient (P = 0.011). There was no reported difference in practice where there is pre-existing malnutrition (P = 0.125) (Table 5.10).

5.4.2.3.1 EN and PN

Respondents were asked whether they used EN '*routinely*', '*occasionally*' or '*never*'. More than a third (37.7%, n = 77) report feeding '*routinely*' with EN, compared to 54.4% '*occasionally*' feeding with EN and 7.8% '*never*' feeding with EN. Upon further analysis, 55.7% of university hospital dietitians reported using EN '*routinely*', compared to 26% of district/ general hospital dietitians. Using χ^2 analysis, there was a significant tendency towards EN in university hospitals compared to district/ general hospitals ($P < 0.0001$). The majority of both groups; university hospital dietitians (91.1%) and district/ general hospital dietitians (80.6%) reported using PN '*occasionally*' or '*never*'. The UK had the highest reported '*routine*' use of EN (53.6%), and the lowest '*routine*' use of PN (12.5%). Table 5.11 summarises reported EN and PN use per country.

Dietitians who reported EN use '*routinely*' (n = 162) were asked what their preferred route is for EN: gastric or jejunal. Most (64.2%, n = 104) reported that jejunal feeding was their preferred route, specifically, 77.8% of Canadian dietitians, 54.2% of Irish dietitians and 43.8% of UK dietitians. Most (70.8%) university hospital dietitians and just over half (57%) of district/ general hospital dietitians reported jejunal feeding as their route of choice.

When asked to identify perceived barriers to EN in their institutions from a pre-defined list (Table 5.12), almost 3 in 4 dietitians (73.5%) reported barriers to EN; 64.3% of UK dietitians, 75.2% of Canadian dietitians and 83.9% of Irish dietitians. Those in university hospitals (65.8%) were less likely than those in district/ general hospitals (78.2%) to perceive barriers

to EN, although this fell outside statistical significance (chi-square, $P = 0.057$). The most commonly perceived barrier was '*medical preference*' (57.8%).

Table 5.10 Dietitians' responses regarding timing of feeding for three given scenarios, compared by institution-type

		University hospital	District/ general hospital	*P*
Severe acute pancreatitis	Feed early	52 (64.8%)	57 (48.7%)	0.015*
	Feed later	27 (34.2%)	61 (51.3%)	
Severe acute pancreatitis with obese-range BMI	Feed early	42 (53.8%)	41 (35.7%)	0.011*
	Feed later	36 (46.2%)	75 (64.3%)	
Severe acute pancreatitis with pre-existing malnutrition	Feed early	69 (87.3%)	94 (78.8%)	0.125
	Feed later	10 (12.7%)	25 (21.2%)	

* Statistically significant

Private and 'other' hospital not included in analyses due to small numbers

Table 5.11 Dietitians' reported use of EN and PN, compared by country

		Ireland	UK	Canada	Total
EN	Routinely	10 (32.2%)	30 (53.6%)	37 (31.6%)	77 (37.7%)
	Occasionally	19 (61.3%)	25 (44.6%)	67 (57.3%)	111 (54.4%)
	Never	2 (6.5%)	1 (1.8%)	13 (11.1%)	16 (7.8%)
PN	Routinely	7 (22.6%)	7 (12.5%)	17 (17.8%)	31 (15.2%)
	Occasionally	20 (64.5%)	42 (75.0%)	88 (86.0%)	150 (73.5%)
	Never	4 (13.9%)	7 (12.5%)	12 (10.2%)	23 (11.3%)

Table 5.12 Dietitians' perceived barriers to use of EN in their institution

Are there barriers to EN in your institution?	Yes (%)	No (%)
	150 (73.5)	54 (26.5)
Please indicate what those barriers are*	**n (%)**	
Medic's preference	118 (57.8)	
Technical difficulty (in placing feeding tubes)	79 (38.7)	
Lack of practice guidelines	61 (29.9)	
EN used in the past, but considered a failure	18 (8.8)	
Insufficient dietitian time	15 (7.4)	
Dietitian's preference	3 (1.3)	

* More than one response allowed

5.4.2.4 Requirements and formula

Dietitians were asked which predictive equations they use to calculate requirements in severe acute pancreatitis. No predefined list was provided and multiple responses were allowed. The most common was Harris Benedict[155] (*n* = 85), and Schofield[156] (*n* = 77). Other methods included Ireton-Jones[157] (*n* = 36) and Mifflin St Jeor[158] (*n* = 9, solely Canadian dietitians). Use of a range of 'simple' caloric estimation equations were also reported, from 11 to 14 kcal per Kg per day (in obesity), to 35kcal per Kg. Semi-elemental/ peptide feed (*n* = 98, 49.2%) was the most commonly cited formula used. Standard formulae were reported in 34.2% (*n* = 68) of cases and elemental in 10.6% (*n* = 21) of cases. The majority (67%, *n* = 70) of those who jejunally feed as first line reported using semi-elemental feeds as first choice

compared to 46.5% (n = 27) of those who feed into the stomach as first line. The most commonly cited drivers of formula choice were evidence/ guidelines (78.3%, n = 155), availability (33.8%, n = 67) and consultant preference (14.1%, n = 28). The least chosen option was cost (7.1%, n = 14).

5.4.2.5 Tube insertion

Those using NJ tubes were asked by which method tubes are inserted in their institutions, and multiple responses were allowed. The most common methods were radiology (n = 95), endoscopy (n = 81) and bedside tube insertion (n = 64). Where bedside techniques were used, dietitians were asked who typically inserts the tubes (more than one response was allowed). The responses were doctors (n = 64), ward nurses (n = 31), specialist nurses (n = 22) and dietitians (n = 5).

5.4.2.6 Additions

Dietitians were asked about their practice regarding specific nutrient additions in acute pancreatitis, choosing from the following list: *Probiotics, pancreatic enzymes, glutamine and micronutrients.* Choices were 'always', 'sometimes' or 'never'.

Only 1.1% (n = 2) reported 'always' using probiotics in EN. The use of probiotics was explored in terms of institution-type. Almost all university hospital dietitians (93.2%, n = 68) stated that they 'never' give probiotics with EN. A lower percentage (79.4%, n = 77) of district/ general hospital dietitians reported 'never' giving probiotics with EN. The majority (71.3%) reported using PERT at least sometimes in EN, with 25.8% using PERT at least sometimes with PN. Regarding glutamine, 1.2% (n = 2) reported 'always' using enteral glutamine with EN, while 8.3% reported using parenteral glutamine 'always' with PN. The use of additions is detailed in Table 5.13.

Table 5.13 Use of additions to EN or PN as reported by dietitians

	Addition	'Always'	'Sometimes'	'Never'
EN	Probiotics	2 (1.1%)	25 (14.2%)	149 (84.7%)
	PERT	15 (8%)	119 (63.3%)	54 (28.7%)
	Glutamine	2 (1.2%)	22 (12.8%)	147 (86%)
	Micronutrients	17 (9.9%)	64 (37.4%)	90 (52.6%)
PN	Probiotics	0	8 (4.9%)	156 (95.1)
	PERT	5 (3%)	35 (20.8%)	128 (76.2%)
	Glutamine	14 (8.3%)	35 (20.7%)	120 (71%)
	Micronutrients	91 (52%)	42 (24%)	42 (24%)

5.4.2.7 Guidelines

The guidelines most commonly cited by respondents are presented in Table 5.14 in order of preference. A minority of dietitians were unaware of guidelines, specifically 12.9% (n = 15) of district / general hospital dietitians and 2.6% (n = 2) of university hospital dietitians. Similar percentages of those who see acute pancreatitis patients regularly (9.2%, n = 13) and those who report seeing them occasionally (10.5%, n = 6) reported being unaware of guidelines.

Table 5.14 Guidelines most familiar to dietitians for the management of acute pancreatitis

Guidelines	n	%
ASPEN guidelines	81	40.7
ESPEN guidelines	58	29.2
Unaware of guidelines	19	9.55
Other	17	8.5
BSG guidelines	15	7.5
INDI reference guide	7	3.5
AGA guidelines	2	1.0

5.4.3 Discussion

5.4.3.1 Summary

Practice guidelines originating from several different sources were summarised and amalgamated into seven common themes against which practice was compared. These themes (parameters 1-7) are discussed below in the context of the survey results.

5.4.3.2 Discussion of results in the context of the management guidelines

5.4.3.2.1PARAMETER 1: Specialist teams

A third of dietitians reported that their teams accept tertiary referrals for acute pancreatitis. However, less than a quarter of dietitians in the UK reported that their institutions have a specialist pancreatic multi-disciplinary team. The figures were lower for Ireland and Canada. Less than a quarter of UK dietitians reported that their teams had an institutional protocol for the management of acute pancreatitis. In Ireland and Canada, the numbers were lower still, although the slightly more favourable UK figures may be due to the proportionally higher number of university-hospital dietitians completing the survey. Even if dietitians were not aware of a management protocol where one existed, one would expect them to be aware of a formal *feeding* protocol. Nevertheless, even fewer dietitians reported the presence of a feeding protocol. It does appear that teams and protocols occur simultaneously; Institutions that accepted tertiary referrals were more likely to have a multi disciplinary team and feeding protocol, although not a pancreatitis management protocol.

The UK guidelines recommended that 'specialists in nutrition' should form part of the team for the treatment of severe acute pancreatitis[18], the evidence for which is of grade C quality. From the survey, it appears that rather than specialising in the management of patients with pancreatic disease, dietitians tend to see pancreatic patients as part of a varied caseload. A minority of dietitians were involved in the care of pancreatic patients as greater than 50% of their clinical caseloads. While this appears suboptimal, there are however no guidelines to specifically recommend appropriate dietetic pancreatic staffing levels.

5.4.3.2.2 PARAMETER 2: Early feeding

Although several guidelines recommended early feeding, only the ASPEN guidelines[78] specified any time frame, stating that a feeding tube should be inserted 'as soon as fluid resuscitation is complete'. Although the ESPEN 2006 guidelines[56] suggested that feeding should be commenced 'as early as possible' (especially in alcoholic acute pancreatitis with malnutrition), the guidelines did not specify a time-frame. Similarly, the 2002 ESPEN guidelines recommended early feeding for complicated disease without defining what was meant by 'early feeding'. However, the same guidelines discussed two studies[159-160] that defined early feeding as <48 hours after presentation. The reason for a failure to provide specifics on the timing of feeding is probably due to the fact that no RCTs have been undertaken to compare early and late feeding in acute pancreatitis. Despite the lack of randomised controlled trials, a systematic review[76] examined whether the timing of nutrition support has an influence on outcomes. Less risk was demonstrated when EN was started within 48 hours of presentation (compared to PN), but there was no difference in the groups when EN was started after 48 hours.

Despite the lack of clarity from the guidelines, most dietitians considered early feeding to be important. Almost all dietitians reported that they consider 'early feeding' to imply feeding in less than 48 hours of presentation. However, dietitians (especially those in district / general hospitals) did not perceive the obese patient to be at as high a priority as the malnourished patient in terms of early feeding. This is not unexpected, as an obese patient may not immediately warrant nutritional concern. However, obese patients with acute pancreatitis may suffer worse clinical outcomes as obesity is a prognostic factor in the development of complications in acute pancreatitis[161-162].

5.4.3.2.3 PARAMETER 3: Enteral feeding

The guidelines have unanimously recommended EN as opposed to PN as first line nutritional therapy in acute pancreatitis so it is surprising that just over a third (37.7%) reported 'routine' use of EN, although when amalgamating the 'routine' and 'occasional' EN feeders, the percentage increased to 92%. Notably, 7.8% of dietitians reported 'never' feeding with EN. Again, practice in university hospital is more consistent with the evidence base - those in

university hospitals are more likely to use 'routine' EN than those employed in district or general hospitals. Among countries, practice in the UK appears to be the most consistent with guidelines, with the highest 'routine' use of EN and the lowest 'routine' use of PN. However, this may be biased by the fact that the UK had the highest proportion of university-hospital dietitians participating in the survey. University-hospital dietitians and UK dietitians were the least likely to perceive barriers to EN. In general, dietitians perceived 'medical preference' to be the largest barrier to EN. The survey did not specify a differentiation between medics who were aware of the guidelines and chose to ignore them, and those that were not aware of the guidelines, as had been done by the Canadian ICU survey in 2004[163].

5.4.3.2.4 PARAMETER 4: Route of feeding

The majority of dietitians surveyed reported using the jejunal rather than gastric route for feeding. Jejunal feeding was more common among university hospital dietitians than district/ general hospital dietitians. However, although the UK had the most university dietitians in the survey, jejunal feeding was most common in Canada and least common in the UK. This UK bias towards gastric feeding may be a reflection of the 2005 UK study in which NJ feeding was compared to NG feeding showing no difference in mortality[65]. In reference to this study, the ESPEN guidelines postulated that acute pancreatitis could not have been very severe in those patients if gastric emptying was maintained. The UK study has been criticised for probably comparing gastric to duodenal rather than jejunal feeding, based on the position of the tube tip. The optimal route of EN continues to be controversial, as is evidenced by the contradictory guidelines. Meanwhile, as jejunal feeding is known to be safe, conferring theoretical benefits in avoiding stimulation of the injured pancreas, it seems wise to feed jejunally where feasible, particularly in severe cases. Barriers to jejunal feeding include difficulty in the insertion of tubes. Part 1 of this Chapter described a study on the blind bedside insertion of NJ tubes by nurses and dietitians. However, dietitian involvement in tube placement is not common-place. Only 5 respondents in this study reported that a dietitian undertakes NJ insertion in their institution.

5.4.3.2.5 PARAMETER 5: Nutritional requirements

Basal metabolic rate increases in severe acute pancreatitis, due to inflammation and pain, leading to an increase in total energy expenditure[56]. It is not feasible to use indirect calorimetry in day to day practice, therefore dietitians utilise predictive equations to calculate nutritional requirements in various clinical situations. There are several available methods to calculate requirements in acute pancreatitis. The most commonly reported prediction equation used was the Harris Benedict[155] equation. However, this practice is questionable given that the Harris Benedict equation is unreliable in the complicated septic patient[55, 58]. There was some regional difference in equations used, with the Mifflin-St Jeor equation[158] being used exclusively in Canada.

5.4.3.2.6 PARAMETER 6: Formula

Peptide-based (semi elemental) formulae were the most commonly used (49.2%) in severe acute pancreatitis, especially by those who feed jejunally (67%). Dietitians were driven in their decision by the evidence-base or by guidelines, and not by cost. In theory, peptide-based regimens should be superior, as they do not rely on the secretion of pancreatic enzymes, and therefore should not exacerbate the injured pancreas. Immuno-enriched formulae containing immune system modulating substrates such as glutamine, arginine, and omega-3 fatty acids may also confer benefits. However, the evidence base to support their use is weak[70].

5.4.3.2.7 PARAMETER 7: Glutamine and other additions

The use of additions to EN and PN formulae tends to occur based on clinical judgment in a given scenario, rather than by guidelines. An example is the use of PERT during EN, or the addition of PERT to tube feeds – for which there is little guidance. The dietitian along with the team usually determines the need for such intervention based on clinical symptoms and the tolerance to feeding. The use of PERT in EN appears to be widespread. Over seven in ten dietitians surveyed use PERT at least 'sometimes' during EN. This area of nutrition support warrants further research.

The guidelines recommended the administration of parenteral glutamine with PN. However there are no guidelines for the provision of enteral glutamine. The survey showed a notable use of glutamine in patients with severe acute pancreatitis, although it is more commonly used with PN than with EN, being used at least 'sometimes' by a third of those surveyed.

Similarly, there are no formal guidelines for the use of probiotics in acute pancreatitis. Nonetheless, there has been much recent attention on this topic. Following the publication of the largest study of probiotics to date[164], the Dutch Acute Pancreatitis Study Group, showed that jejunal infusion of probiotics more than doubled mortality compared with placebo in 298 patients with predicted severe acute pancreatitis. Therefore, it was surprising that 1.1% of dietitians reported 'always' using probiotics with EN, while 14.2% reported 'sometimes' using probiotics with EN. Clearly, there is a need for exhaustive and detailed guidelines, thorough dissemination, and extensive clinical updates to ensure evidence-based practice.

5.4.3.3 The use of management guidelines

Reflecting the quantity of guidelines available, dietitians reported a variety of guidelines when asked with which guidelines they were most familiar for the nutritional management of acute pancreatitis. Not surprisingly, guidelines produced by working groups of the two major nutrition bodies; ASPEN[78] and ESPEN[56] were the most commonly cited. Most respondents that were unaware of guidelines were from district or general hospitals.

5.4.3.4 Other studies comparing practice to guidelines

While several other studies have investigated the management of patients with acute pancreatitis, only one other examined dietetic practice. Greenwood and colleagues surveyed critical care dietitians at ICUs of greater than 8 beds in Canada in 2004[163]. The survey consisted of 13 questions, and of 62 ICUs contacted, 54 responded. They showed that while the majority of ICUs provided EN to patients with acute pancreatitis – consistent with the ASPEN guidelines - 15% of units reported never providing EN to patients with acute pancreatitis. They also identified a 'questionable' pattern of PN usage. Most respondents

reported using PN quite routinely. The practice of initiating PN concurrently to EN for a week or less was widespread. The authors also identified barriers to EN similar to the results of the current study. The most common barrier was 'technical difficulty in accessing the small bowel' (72%), followed by lack of support from medical/surgical staff. They differentiated between medical / surgical staff who were aware of the guidelines but opted to ignore them (47%) and those who were not aware of the literature (38%).

While a survey of dietitians has the advantage of accessing professionals immersed in the nutritional management of patients, the dietitian's preferred management may be at odds with that of the team, and therefore the practice, perception and views of medics and surgeons on the nutritional care of patients with acute pancreatitis should be considered.

One study aimed to verify the knowledge and acceptance of guidelines for the management of acute pancreatitis among German surgeons[165]. This survey focussed on the medical and surgical management of acute pancreatitis, such as the use of prophylactic antibiotics and the timing of surgery, rather than nutrition. While the medics / surgeons were aware of the management guidelines, the guidelines were not strictly followed in all cases. In a separate survey of German gastroenterologists involved in the treatment of patients with acute pancreatitis, ten questions were asked based on eight management guidelines[166]. Although the survey focussed mainly on medical / surgical rather than nutritional management, the participants were asked about the use of EN. Three in four respondents reported using EN over PN.

In a study of nutritional practice undertaken in Australia and New Zealand, ICUs were surveyed to determine the nutritional therapy practices of patients with severe acute pancreatitis requiring critical care[167]. This survey enrolled patients and followed their treatment rather than ascertaining specific professionals' practices or perceptions. While EN was commonly used (42%) as the initial therapy, PN was more frequently used (57%). The authors recommended improved education and guideline dissemination given that the management guidelines recommend EN as the initial feeding modality[167].

The development of management guidelines is a costly process in terms of time and resources and requires a significant investment by the authors in the research, assimilation, preparation, review and presentation of the data. However, this process is essentially

meaningless unless the management guidelines are put into use by the clinicians for whom they are intended. There may also be an element of guideline-fatigue. A US pancreatologist wrote that there are an overwhelming number of acute pancreatitis guidelines and that "competing practice guidelines clamour for attention and respect"[168]. However, in situations where guidelines are not followed, the lack of implementation may be due to a lack of resources rather than by a choice by clinicians to ignore them, and the areas most likely to be ignored are those for which there is the weakest evidence-base[168].

There has been little research on whether the guidelines in acute pancreatitis truly change practice (such as an evaluation of practice prior to and following the introduction of guidelines). One such study evaluated the impact of the introduction of the Japanese guidelines for the management of acute pancreatitis in 2003[169]. They found that the proportion of EN use increased significantly from 9% to 28% in severe acute pancreatitis following publication of the guidelines. They also divided the group into those who had read the guidelines (including full-text, tables or flow-charts) or not, and the proportion of those who began EN was higher among those who had read the guidelines[169]. This study indicates that management guidelines do impact practice, but that reading of the guidelines, even of tables and visuals aids such as flow charts, is crucial for guideline adherence. The development of visual flow-charts and algorithms of care for display in individual institutions may aid in the dissemination of guidelines.

5.4.3.5 Study limitations

- It was not possible to determine a percentage response rate, as the numbers of dietitians working in pancreatic disease was unknown
- There may have been an element of non-representativeness of the findings of this study due to selection bias. Response was proportionally highest in Ireland, likely due to the fact that the survey was co-ordinated from Ireland. Response was proportionally lowest in the UK. How this affects interpretation is unclear, however, as university hospital responses were higher from the UK, this introduces an obvious bias

- Due to its nature as an anonymous electronic survey, an assumption is made that the information provided is accurate
- As the survey was voluntary, this may introduce response bias
- Targeting doctors or surgeons would be useful for reporting the existence of protocols, particularly pertaining to medical management. However, one could argue that a protocol should be visible by all members of a multidisciplinary team

5.4.3.6 Study strengths

- This study is the largest study of dietetic practice in acute pancreatitis
- This survey of dietitians was the first to examine clinical practice compared to the guidelines for acute pancreatitis in Ireland and the UK
- By including Ireland, the UK and Canada, a comparison per country was possible
- By including those who do not commonly see patients with acute pancreatitis, or who work in district or general hospitals, a comparison of practice per institution was possible
- The survey spanned different areas of practice, including the existence of teams and protocols, the use of EN and PN, and the provision of specific nutrient additions
- Dietitians' perceptions of barriers to best-practice were also assessed

5.5 General conclusions

Part 1 of this Chapter showed that the adoption of the practice of blind bedside feeding tube insertion is a safe, simple technique and a feasible expansion of the role of the dietitian and nurse within a specialist team. This initiative conferred significant economic advantage, as well as reducing the need for specialist personnel and equipment. By ensuring timely placement of feeding tubes, this initiative had direct effects on patient care by reducing the need for unnecessary transfer to other hospital departments and the avoidance of delays in starting a prescribed feeding regimen. For patients with severe acute pancreatitis, this is an important factor in ensuring best clinical practice.

Part 2 of this Chapter described a local review of nutrition support in patients with severe acute pancreatitis. The nutritional and clinical management guidelines in acute pancreatitis provide a template against which practice in acute pancreatitis may be evaluated, as well as providing a recommendation to undertake prospective audits of practice. This audit provided data for a three-year period which identified both shortcomings and strengths in management. In particular, a low overall mortality was apparent, as well as compliance in the routine use of EN. Improvements in the delay in establishing feeding over the audit period were demonstrated, and deficiencies in some aspects of aetiology determination and data collection were highlighted. Audits are a key factor in achieving improvements in clinical care. This should be done both locally (single-institution audits such as this one), regionally, nationally and internationally. While audits are important in measuring actual practice against guidelines, surveys of professionals can aid in determining practice patterns, perceptions and barriers to change. A survey of dietetic practice, perceptions and barriers to acceptance of the guidelines was therefore identified as the next step in improving nutritional practice in this disease.

Part 3 of this Chapter followed on from the finding of Part 2, by aiming to measure the nutritional management of patients with acute pancreatitis throughout Ireland, as well as in the UK and Canada. Findings from Part 3 provided a platform for improvements in clinical care by highlighting clinically important gaps between guidelines and practice. Education strategies must be appropriately tailored to overcome barriers to best-practice. This should involve dissemination of results at the Pancreatic Society of Great Britain and Ireland,

Digestive Diseases Federation, The British Society for Enteral and Parenteral Nutrition, and the Irish Society for Enteral and Parenteral Nutrition meetings. Future research should focus on grey areas in pancreatitis management, with a view to strengthening the level of evidence available in the guidelines. This will advance the nutritional management of acute pancreatitis and ultimately enhance patient care.

5.5.1 Lead-in to following studies

To conduct an investigation of practice and clinical management in *chronic pancreatitis* compared to the guidelines (as was done in the present chapter for *acute pancreatitis*) would be neither feasible nor useful due to the scarcity of practice guidelines. Moreover, the deficiencies in care highlighted for patients with acute pancreatitis must be assumed to be at least equivalent for patients with chronic pancreatitis. Therefore, to address these gaps clinical practice and research, a cohort study was designed to which patients were recruited for nutritional assessment. Specifically, two main areas of chronic pancreatitis nutritional management were targeted: 1) malnutrition and nutrient deficiency (Chapter 6), and 2) bone health (Chapter 7).

Chapter 6 An investigation of nutritional status, exocrine function, endocrine function, pain and social issues in chronic pancreatitis

This chapter describes the first phase of a cohort study and investigated malnutrition, vitamin deficiency, endocrine status and exocrine status in patients with chronic pancreatitis. The second phase is described in Chapter 7.

6.1 Introduction

6.1.1 Malnutrition in chronic pancreatitis

Patients with chronic pancreatitis are high risk for the development of nutrition-related complications. PEI resulting from progressive loss of pancreatic tissue ultimately causes maldigestion and malabsorption of nutrients. This loss of nutrients from the gut coupled with poor diet, increased requirements, and often, heavy smoking and drinking, results in the development of debilitating symptoms, nutrient deficiencies and depleted muscle mass. Social circumstances may further exacerbate nutritional status, and QOL may be reduced. DM in chronic pancreatitis tends to be associated with poor glycaemic control and a high risk of hypoglycaemia. The nutritional management of patients is fraught with difficulty, as various factors co-exist resulting in a complex nutritional situation. Correction of PEI with PERT is the mainstay of treatment, and high-level evidence in this area has demonstrated its effectiveness in reducing steatorrhoea and other malabsorptive symptoms[170]. The characterisation of malnutrition, nutrient deficiency, and pancreatogenic DM are less studied areas and therefore, dietary management tends to be unstructured and *ad-hoc*.

6.1.2 Fat soluble vitamin deficiency in chronic pancreatitis

The ESPEN guidelines on acute and chronic pancreatitis reported that deficiencies of fat-soluble vitamins are common and recommended supplementation where clinically indicated[56]. However, with the exception of vitamin D[171-172], the studies underpinning these guidelines were largely published in the 1980's and 1990's[100-103]. Since then, there has been

little attention given to nutritional deficits in chronic pancreatitis despite the obvious nutritional risk factors. These older studies on fat-soluble vitamin deficiency in chronic pancreatitis reported a high prevalence of deficiency[100-101] of up to 75%. Prior to the completion of this study, no other studies had been published on the prevalence of fat-soluble vitamins in chronic pancreatitis. Clinical or subclinical vitamin deficiencies may result in long-term health issues including visual deficits[173], neurological deficits[102], and poor bone health[109, 174]. Early detection and treatment would serve to lessen the risk of such deficiencies; however micronutrient screening is unlikely to be part of routine management for most patients and therefore nutrient deficiencies are likely to remain undetected and untreated until overt clinical symptoms appear.

6.1.3 Exocrine status and PERT

6.1.3.1 PEI

Pancreatic fibrosis, acinar atrophy, chronic inflammation, and blocked pancreatic ducts are key pathological features of chronic pancreatitis[33]. The progressive deterioration of pancreatic parenchyma leads to eventual impairment of exocrine (and endocrine) function, and subsequent malabsorption[116]. Maldigestion and malabsorption are relatively late clinical manifestations of chronic pancreatitis, and are thought to occur only when pancreatic enzyme output is reduced to <10% of normal secretion[175]. In general, fat malabsorption occurs earlier and is more clinically evident than that of protein and carbohydrate. This is because lipase suffers irreversible inactivation at an acidic pH, which occurs frequently in chronic pancreatitis owing to a reduction in pancreatic bicarbonate production[176].

6.1.3.2 Diagnosis of PEI

Although considered the gold standard, direct investigation of pancreatic exocrine function by duodenal intubation is invasive and impractical necessitating indirect tests. Although the perfect test does not exist, the faecal elastase-1 test is the most popular method of assessing PEI at present[177]. Benefits of faecal elastase-1 include the following: it is easy to perform; PERT does not need to be discontinued for testing; a single stool sample is needed (which is

stable at room temperature for several days[178]); patients do not need to take a special diet or substrate prior to testing; and it is relatively cheap and widely available. In severe PEI, the sensitivity is 100%, but it is less sensitive for mild to moderate PEI (77-100% sensitivity for moderate PEI, 0-63% for mild PEI[177]). It has a specificity of about 93%[179]. In practice, a trial of PERT to establish any improvement in symptoms is a commonly used method[4]. PERT is the cornerstone for treatment for PEI[180] and several studies have demonstrated the efficacy of PERT for reducing symptoms of malabsorption in chronic pancreatitis[170, 181].

6.1.4 Endocrine status and pancreatogenic diabetes

As a major endocrine gland, the pancreatitis has a key role in glucose homeostasis. Among the hormones secreted by the pancreas are insulin, glucagon, pancreatic polypeptide and somatostatin. Incidence varies from 30-50%[88] in general, and depends on several factors, including aetiology, the presence of pancreatic calcifications[182] and the duration of disease. Insulin and glucagon secretion are disturbed more strongly in calcific than non-calcific pancreatitis[183]. Prior to undertaking this study, little attention had been given to pancreatogenic DM in the literature. Few studies or guidelines had sought to characterise the disease, or provide a framework for management.

6.1.5 Pain in chronic pancreatitis

Pain represents the most common and difficult-to-treat feature of chronic pancreatitis resulting in an inordinate degree of disability and an estimated cost (in the USA) of more than US $ 638 million[184-185]. In a survey of chronic pancreatitis patients of seven countries in the Asia-Pacific region, 60-100% of patients had pain[41]. Patients typically complain of epigastric pain that radiates to the back. The pain may worsen post-prandially, and may be associated with nausea and vomiting[186]. The pathophysiology of pain in chronic pancreatitis is complex and poorly understood, and no current intervention provides complete relief from pain for all patients[184]. Researchers from the NAPS-2 (North American Pancreatitis study-2) consortium suggested that pain is best classified as 'constant' or 'intermittent', rather than by severity, as the temporal pattern of pain may have a more profound impact on patients

and outcomes.[184] The first line of treatment for chronic pancreatitis pain is lifestyle adjustment, followed by analgesics[186]. Alcohol abstinence is recommended for all patients regardless of aetiology. This may result in improvements in pain and survivals rates, although unproven by prospective trials. Where lifestyle changes and analgesics fail to control pain, interventional management may be indicated, such as stenting, lithotripsy, surgery or spinal cord stimulation[186]. Studies on antioxidant therapy for reduction of pain have shown variable results. The theory underpinning antioxidant therapy is that free radical-induced pancreatic damage causes intractable pain, which may be alleviated by taking a combined antioxidant preparation (containing large doses of selenium, beta-carotene, L-methionine, ascorbic acid and d-alpha tocopherol acetate). Improvements demonstrated in one study[122] regarding QOL, pain and working days lost were contradicted by a recent RCT[123] which failed to show any improvements in QOL or pain, despite increases in serum levels of antioxidants. Although the role of PERT in managing PEI is well-established, it remains unclear whether or not PERT has any effect on pain. Nevertheless, the AGA recommended that a trial of 'high-dose' PERT with acid suppression for pain management should be given prior to commencement of narcotics or invasive interventions[180, 187].

6.1.6 Social issues in chronic pancreatitis

Since commencement of the current study, several studies have reported on the social aspects of chronic pancreatitis. Issues of concern include difficulty in maintaining employment[188], reduced QOL (correlated with pain scores)[189], long hospital stays[190], and continued alcohol intake and smoking. There is a need for greater appreciation by the multidisciplinary team of the negative effect of these social issues on patients' health and wellbeing, as well as the effect on nutritional status.

6.1.7 Study rationale

Patients with chronic pancreatitis are at a high risk of malnutrition for many reasons. However studies on nutrition in chronic pancreatitis are not plentiful. For example, most of the studies on vitamin deficiency in chronic pancreatitis were published several decades ago.

While a few studies have examined malnutrition, anthropometry, exocrine/ endocrine dysfunction and pain in chronic pancreatitis, none have been published from Ireland and few from the UK. How best to define and assess nutritional status in this group has not been well-characterised. There is a lack of clarity around the prevalence and degree of vitamin deficiency. As was described in Chapter 2, little is known regarding the prevalence of pancreatogenic diabetes in a Western European chronic pancreatitis group, or the extent to which glycaemic control is deranged. The prevalence of PEI is similarly unknown, as is the use of PERT and the adequacy of enzyme therapy. An examination of the type and frequency of pain and adverse symptoms would help in the clinical evaluation of patients. By characterising the nature of malnutrition and associated complications in chronic pancreatitis, protocols for assessment and management of patients may be formulated to optimise nutritional status and therefore improve overall health.

6.1.8 Study hypothesis

Patients with chronic pancreatitis have nutritional deficits compared to matched controls.

6.1.9 Study objectives

1. To investigate malnutrition in chronic pancreatitis, specifically BMI, body composition and the relationship between albumin and nutritional status
2. To determine the prevalence of fat-soluble vitamin deficiency in chronic pancreatitis compared to matched controls, specifically vitamins A, D, and E.
3. To measure exocrine function and to determine usage of PERT in chronic pancreatitis
4. To measure endocrine function and the prevalence of pancreatogenic diabetes in chronic pancreatitis
5. To determine the occurrence of adverse symptoms and to examine the relationship between patterns of pain and clinical features of chronic pancreatitis
6. To examine social factors in chronic pancreatitis including hospital admissions, employment status, smoking and alcohol

7. To develop an evidence-based tool for PERT, DM and over nutritional management of chronic pancreatitis

6.2 Materials and methods

6.2.1 Study description

In this prospective, controlled cohort study, patients attending The Centre for Pancreatico-Biliary Diseases, Tallaght Hospital (a university-affiliated, tertiary pancreatic referral centre) with a diagnosis of chronic pancreatitis were invited to attend for an assessment. Diagnosis of chronic pancreatitis was made based on clinical and radiological data, and disease severity (according to the Cambridge classification[130]), and aetiology were determined by the pancreatic team. An aetiology of alcohol-induced chronic pancreatitis was recorded where alcohol intake exceeded recommended intakes in the absence of other causes.

6.2.2 Recruitment

6.2.2.1 Patient recruitment

This study represents the first phase of a 2-phase study on nutrition in chronic pancreatitis. Phase 2 investigated osteoporosis in the same cohort of patients and is described in Chapter 7. Demographics and other basic data are common between the two phases, as are assessment details. Details on assessment are provided in Chapter 4 and are described here in brief. Eighty-four Caucasian patients with chronic pancreatitis were identified as eligible for the study from an existing department pancreatic database. Of these, 22 were excluded (repeated failure to attend appointments, declined to participate, inability to contact). In total, 62 patients participated in the assessment. Patients were invited to attend an out-patient clinic and were not acutely unwell at the time of assessment. Patients had neither history of other malabsorptive conditions (such as coeliac disease or IBD) nor a history of GI surgery. See data collection form in Appendices H and I.

6.2.2.2 Control recruitment

As controls, 66 healthy men and women were recruited and were not paid for participation. Controls were recruited from the same urban area as the patients, and were matched for age, gender and education level. Of these, less than half were recruited from a variety of staff within our institution, and the remainder were workers recruited from local manufacturing and transport centres. Controls with any malabsorptive conditions or history of GI resection were excluded. The study was advertised using leaflets and posters and *via* human resource departments.

6.2.3 Assessment

6.2.3.1 Anthropometry

Height and weight were measured, from which BMI was calculated. BMI was classified according to the WHO classification (see Chapter 4). Prior to being weighed, patients were asked to report their weight of '1 year ago'. Depending on weight change over 1 year, for analysis patients were classed as '*weight losing*' (net weight loss over the previous year) or '*weight stable/ gaining*' (net weight gain or stable weight over the previous year). To measure muscle mass, MAMC was constructed from MUAC and TSF, a measure of body fat. TSF was done using Lafayette Skin fold Calliper II (Lafayette Instrument, UK) and expressed in mm. The average of three measurements was taken[127]. Values were compared to original reference guides published by Bishop and colleagues[127] for both sexes separately. MAMC was calculated from MUAC and TSF using the following equation:

. Handgrip strength was measured using a Jamar hand dynamometer and expressed in Kg (Chapter 4).

6.2.3.2 Biochemistry

Standard bloods tests included liver function tests, CRP (mg/L), HbA_{1c} (%), albumin (g/L) and glucose (mmol/L). Vitamin D was measured as the inactive metabolite 25-OH D by LC-tandem mass spectrometry. Serum vitamins A (measured as retinol) and vitamin E (measured as α-tocopherol) were measured by high performance liquid chromatography. Cholesterol and

triglyceride were measured and the ratio of vitamin E concentration to the sum of cholesterol and triglyceride concentrations was calculated as *vitamin E:lipid ratio*. Institutional reference ranges for vitamins were employed as follows: vitamin A, 1.6 – 3.7 µmol/L; vitamin E, 21.3 – 43.8µmol/L; vitamin E: lipid ratio, 3.8-6.3µmol/L; vitamin D deficiency <25nmol/L, vitamin D insufficiency <80nmol/L. Patients were asked to report all current or recent usage of nutritional supplements.

6.2.3.3 Exocrine function

To assess exocrine function, 46 of 62 patients provided a stool sample for the measurement of faecal elastase-1 which was measured using an enzyme-linked immunosorbant assay (ScheBo® pancreatic elastase-1 stool test), and was expressed as µg / g stool. Normal pancreatic exocrine function was >200 µg / g, mild PEI was 100-200 µg / g and severe PEI was <100 µg / g (Chapter 4). Use of PERT was noted and the dosage of enzymes were recorded (total per day, and per Kg body weight).

6.2.3.4 Endocrine function

As well as HbA_{1c} and glucose, a prior diagnosis of DM was noted if applicable. If subjects were diabetic, the mode of control was recorded: diet only, oral hypoglycaemic agents (OHA), or insulin.

6.2.3.5 Adverse symptoms and pain

Subjects were asked if they regularly suffered from symptoms from a pre-determined list: abdominal pain, diarrhoea, steatorrhoea, loss of appetite, vomiting or taste disturbances. Additionally, patients were asked to describe any other regular adverse symptoms. Regarding pain, subjects were asked if they had any pain on the day of assessment. Typical pancreatic-type pain (epigastric, radiating to the back) was described. Patients were asked to described the severity of pain based on a ten-point visual analogue scale (0= *'no pain'*, 10= *'worst pain you can imagine'*) (Appendix J). Subjects were further asked to describe the nature of their pain: *'constant'* or *'occasional'*. Use of pain medications was noted.

6.2.3.6 Hospital admissions and social factors

Hospital admissions in the year prior to assessment were recorded using electronic hospital inpatient records (Patient Identity Management System, PIMS). The number of admissions and total number of days were recorded. Only admissions to Tallaght Hospital were included, including any time spent in the accident & emergency department. However, day cases were excluded. For analysis, hospital admissions were retrospectively categorised as 'none', '1-2' or '3 or more'[184]. Patients were asked if they were in employment or not, and if not, whether this was due to retirement, social reasons, or as a consequence of chronic pancreatitis. Smoking status was recorded at interview for all participants and classed as current, ex or never smokers. For former or current smokers, a mean pack year was calculated. One pack year corresponded to 20 cigarettes per day for one year. Alcohol intake was quantified in units of alcohol (1 pint equivalent to 2 units, 1 standard glass of wine equivalent to 1.5 units, 1 standard measure of spirits equivalent to 1.5 units).

6.2.4 Statistics

Student's T-test was used to compare parametric data, and χ^2 for categorical data. Continuous data were divided into tertiles for comparison where appropriate. One-way analysis of variance (ANOVA) was performed to compare group means and *post-hoc* (Tukey) analysis was completed where appropriate. Independent variables were correlated using Pearson's correlation. Where mean was given, SD was given in parenthesis. For all analyses, *P* values were two-sided, and a *P* value of <0.05 was considered statistically significant. Statistical analyses were done using Minitab, version 15.1 (State College, USA).

6.2.5 Ethical approval

Ethical approval was given by the Joint Tallaght hospital / St James Hospital Ethics Committee (Appendix D).

6.3 Results

6.3.1 Demographics

Patients and controls were well-matched for sex, age and socio-economic status (Table 6.1). Forty-five (72.6%) of the patients were male, compared to 48 (72.7%) of the controls (P = 0.98). Mean (SD) patient age was 47.9 (12.5) compared to a mean (SD) control age of 47.7 (11) (P = 0.922). Twenty-two patients (35.5%) had competed 3rd level education or higher, compared to 26 (39.4%) controls (P = 0.65). Regarding disease severity, 17 patients (27.4%) were classed as 'severe' and 22 (35.5%) patients as 'moderate', with the rest being classed as 'mild'. Alcohol was the aetiology of disease in 38.7% of cases. 'Other' aetiologies included gallstones, hyperlipidaemia and steroid-induced chronic pancreatitis.

6.3.2 Anthropometry and hand-grip strength

Anthropometry results are detailed in Table 6.2. In men, BMI was significantly lower in patients than controls (P = 0.007). The BMI of female patients and controls were statistically similar. Although half of male chronic pancreatitis patients were overweight or obese, the prevalence of overweight / obesity was lower than among controls. BMI did not differ for patients across disease severity grades (ANOVA, P = 0.85). Fat stores (TSF) were lower in patients of both sexes compared to controls. Muscle stores (MAMC) were lower in males (P = 0.001). Hand-grip strength was significantly lower in male patients than in controls (P = 0.048). Although handgrip strength was not correlated to BMI (R= 0.04, P = 0.779), patients who were 'weight losing' had significantly lower handgrip strength than those who had gained weight or stayed stable in the year prior to assessment, for all BMIs (P = 0.016). Handgrip strength was significantly lower among older patients (R= -0.431, P = 0.006).

Table 6.1 Demographic details of patients with chronic pancreatitis and controls

		Chronic pancreatitis	Controls	*P*
Sex , n (%)	Male	45 (72.6)	48 (72.7)	
	Female	17 (24.4)	18 (27.3)	0.985
Age	Mean (SD)	47.9 (12.5)	47.7 (11)	0.922
Education level completed, n (%)	Primary or secondary	40 (64.5)	40 (60.6)	
	Third level or higher	22 (35.5)	26 (39.4)	0.65
Marital status	Single	19 (30.6)	10 (15.1)	
	Married, co-habiting	32 (51.6)	51 (77.3)	0.01*§
	Divorced, separated, widowed	11 (17.8)	5 (7.6)	
Disease severity, n (%)	Mild	23 (37.1)	-	-
	Moderate	22 (35.5)		
	Severe	17 (27.4)		
Aetiology, n (%)	Alcohol	24 (38.7)		
	Idiopathic	12 (19.3)	-	-
	Pancreas Divisum	2 (3.2)		
	Hereditary / genetic	4 (6.4)		
	Other	11 (17.4)		
	Unknown	11 (17.4)		
Years since diagnosis	Mean (SD)	5.4 (6.5)	-	-
	Range	0-36		
Pancreatic calcifications	Yes	13	-	-
	No	49		

* Statistically significant , §Chi-squared = 9.277, DF = 2

Table 6.2 Anthropometry for patients with chronic pancreatitis compared to matched controls

	Male			Female		
	Patient	*Control*	***P***	*Patient*	*Control*	***P***
BMI (Kg/M^2) mean	25.9 (4.9)	28.5 (4.2)	0.007*	25.5 (5.4)	26.7 (3.5)	0.422
[β]Overweight/ obese, n (%)	24 (53.3)	39 (81.3)	0.038*[§]	7 (41.2)	12 (66.7)	[#]
TSF (mm)	7.7 (5.3)	12.5 (6.6)	<0.001*	11.3 (7.6)	21.4 (6.7)	0.001*
MUAC (cm)	29.0 (3.4)	32.4 (2.9)	<0.001*	27.4 (4.1)	30.3 (3.4)	0.046*
MAMC (cm)	26.6 (2.9)	28.5 (2.3)	0.001*	23.9 (3.1)	23.6 (1.7)	0.763
Handgrip strength (Kg)	39.9 (7.7)	43.3 (7.7)	0.048*	25.9 (7.3)	26.3 (5.7)	0.865

*Statistically significant difference, [β]Includes both overweight and obese BMI groups (BMI $\geq$25 Kg/M^2), [§] Pearson's χ^2 test shows difference between all BMI categories, [#]P-value unavailable due to small cell counts

6.3.3 Albumin

There was a statistically significant relationship between albumin and disease severity. Albumin levels were significantly lower in those with severe disease than in those with mild disease (P = 0.019), there was no significant difference between those with mild and moderate, or moderate and severe disease (Figure 6.1). Albumin levels were also lower in underweight patients compared to both normal BMI and overweight/obese patients (P = 0.003). There were positive correlations between albumin and serum vitamin A (R = 0.532; P = 0.000, Figure 6.2), vitamin E (R = 0.335; P = 0.013) and vitamin D (R = 0.253; P = 0.049), but not albumin and vitamin E: lipid ratio. However, although all were statistically significant, only the correlation between vitamin A and albumin (Figure 6.2) was of moderate strength with the other being weakly correlated. Bearing in mind that serum vitamin level and albumin may both be affected by systemic inflammation, multivariable analysis was undertaken to control for the effect of inflammation, measured by CRP. On multivariable

analysis, vitamins A, E, CRP and age were all independently predictive of serum albumin (lower vitamin levels associated with lower albumin / higher age and CRP associated with lower albumin). Therefore, low serum albumin was associated with low serum levels of vitamins A and E, independent of the inflammatory state (Table 6.3).

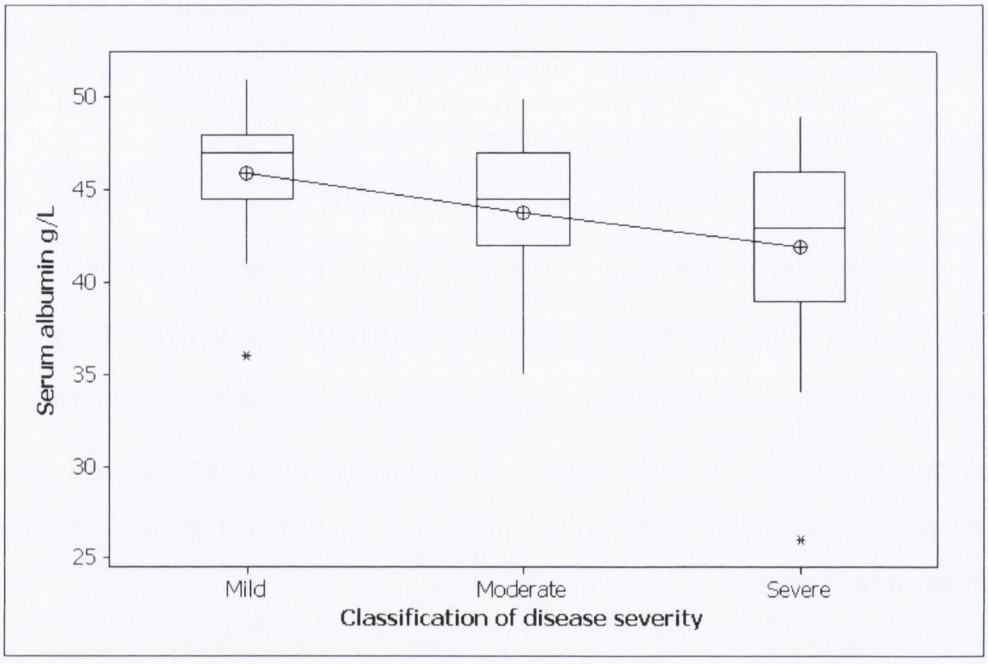


Figure 6.1 Box plots comparing serum albumin levels among disease severity grades (Cambridge classification)

ANOVA, $F(2, 58) = 4.27$, $P = 0.019$

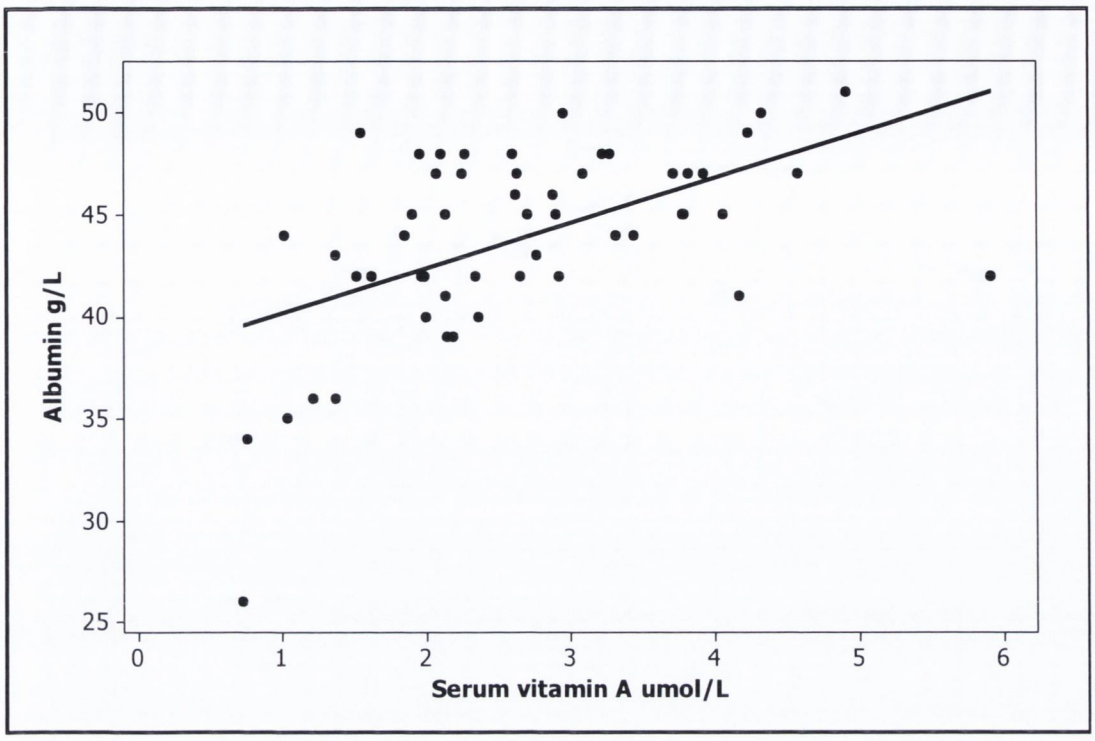


Figure 6.2 Correlation between serum albumin and vitamin A

Pearson's correlation 0.532, $P < 0.0001$

Table 6.3 Backwards, stepwise linear regression showing factors independently predictive of serum albumin

	Coefficient	*P*
Constant	41.4	0.000
Vitamin E	0.12	0.045
Vitamin A	1.3	0.04
CRP	-0.15	0.024
Age (tertiles)	-1.89	0.026

6.3.4 Vitamin deficiency

6.3.4.1 Vitamin A

Vitamin status is detailed in Table 6.4. Although vitamin A deficiency was a feature of both groups, it was more common among chronic pancreatitis patients (14.5%) than controls (6.1%) (Figure 6.3). There was a significant relationship between vitamin A status and BMI; underweight patients had the lowest serum vitamin A levels, while overweight/ obese patients had the highest serum vitamin A levels (ANOVA, $P = 0.017$) (Figure 6.4). Those with alcohol-induced pancreatitis had lower mean (SD) vitamin A (2.34 μmol/ L (1.0)) than those with pancreatitis of other aetiologies (2.9 μmol/ L (1.2)), $P = 0.045$). However, vitamin A *excess* (toxicity) occurred more frequently in patients than controls (19.4% and 1.5% respectively), and was more common than vitamin A deficiency. To determine the reasons for excess vitamin levels, further subgroup analysis was performed. In all, 12 patients had vitamin A excess, of which only 2 were taking multivitamins or fish oil supplements at the time of assessment (compared to 7 patients without vitamin A excess who were taking such supplements). Those with excess serum vitamin A had neither significantly higher levels of liver enzymes, nor significantly higher BMI.

6.3.4.2 Vitamin E

Ten percent of patients had deficiency of vitamin E, although when vitamin E was more correctly expressed as a ratio of blood lipid, deficiency increased to 24.3%, higher than deficiency rates among controls (3.2%). Unlike for vitamin A. there was no significant relationship between categories of BMI and vitamins E:lipid, nor was there an association between aetiology and vitamin E:lipid. Only a minority of patients had vitamin E toxicity, however, patients with vitamin A toxicity were statistically more likely to also have higher vitamin E levels ($P = 0.02$).

6.3.4.3 Vitamin D

'Insufficiency' of vitamin D was the most common vitamin abnormality, and was not statistically different between patients (93.5%) and controls (83.3%) (see Table 6.4). There

was no significant relationship between categories of BMI and vitamins D, nor was there an association between pancreatitis aetiology and vitamin D.

6.3.4.4 Clinical symptoms of deficiency

There were no cases of overt clinical deficiencies for vitamins A or E (e.g. visual or neurological disturbances), nor were there any clinical cases of vitamin D deficiency (e.g. osteomalacia.

Table 6.4 Prevalence of deficiency and excess of vitamins A, E and D among patients and controls

		Patients (n=62) n (%)	Controls (n=66) n (%)	*P*
Vitamin A µmol/L				
<1.6	Deficiency	9 (14.5)	4 (6.1)	
1.6 - 3.7	Normal	41 (66.1)	61 (92.4)	0.001§*
>3.7	Excess	12 (19.4)	1 (1.5)	
Vitamin E µmol/L				
<21.3	Deficiency	6 (9.7)	1 (1.5)	
21.3 - 43.8	Normal	45 (72.6)	53 (85.5)	0.095§
>43.8	Excess	11 (17.7)	8 (12.9)	
Vitamin E:Lipid ratio µmol/L				
<3.8	Deficiency	15 (24.2)	2 (3.2)	
3.8 - 6.3	Normal	44 (71)	58 (92.1)	0.003§*
>6.3	Excess	3 (4.8)	3 (4.7)	
Vitamin D nmol/L$^{\mu}$				
<25mmol/L	'Deficiency'	7 (11.2)	10 (15.2)	
<80mmol/L	'Insufficiency'#	58 (93.5)	55 (83.3)	0.434$^{\mu}$

*Statistically significant, µStudent's T-test, §Pearson's χ^2 test, µinstitutional reference range, #Insufficiency group includes all under 80 nmol/L including 'deficiency' subjects

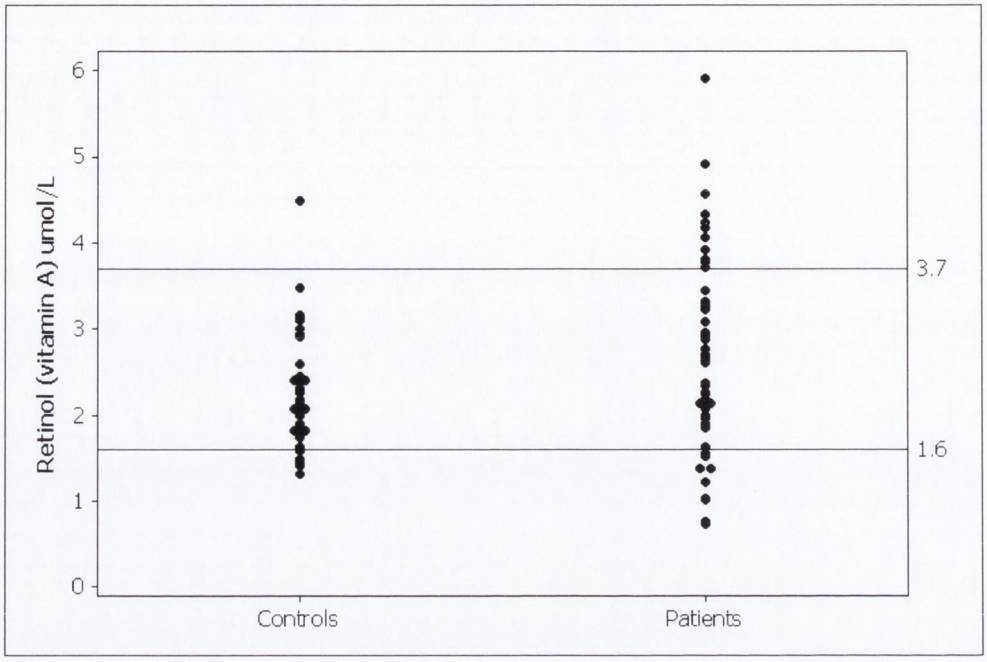


Figure 6.3 Serum vitamin A (retinol) levels for chronic pancreatitis patients and matched controls compared to institutional reference range

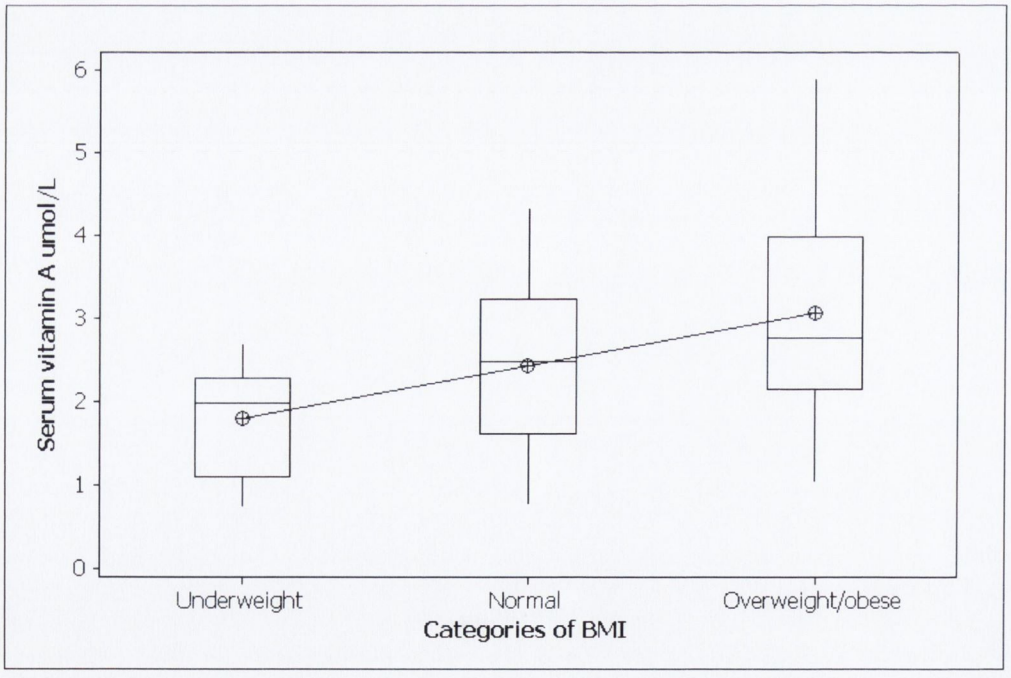


Figure 6.4 Box plots comparing serum vitamin A (retinol) levels among BMI categories

ANOVA $F(2,50) = 4.41$, $P = 0.017$

6.3.5 Exocrine function

'Malabsorption' was a commonly reported symptom among patients (61.7%). A third (16/46) of patients who provided a faecal sample had faecal elastase-1 below normal, and of these, twelve had levels below 100 μg / g, suggesting severe PEI. Faecal elastase-1 was lower in patients with 'severe' chronic pancreatitis compared to those with 'mild' or 'moderate' disease (CI -332.3, -97.2) (P = 0.001), however there appeared to be no relationship between faecal elastase-1 levels and deficiencies of vitamins A, D or E (Table 6.5). There was no significant difference in faecal elastase-1 levels between those reporting pain on the day of assessment or not, or between those with DM or not. There was no difference in mean faecal elastase-1 levels between those with alcohol-induced pancreatitis and those with pancreatitis of other aetiologies (P = 0.14). Over half (51.6%) of patients were taking PERT. Of those, 15 patients reported taking up to 60,000 U lipase daily, while 17 patients reported taking greater than this amount (up to a maximum of 170,000 U lipase daily). The mean (SD) PERT dosage taken daily (among those taking PERT) was 66,938 (37,744) U lipase (median (67,500 U lipase). Per Kg weight, the mean PERT taken was 938.6 (482) U lipase, with a range of 133.3 to 2005.3 U lipase. There was no correlation between faecal elastase-1 levels and the dosage of PERT (P = 0.103).

6.3.6 Endocrine function

Among chronic pancreatitis patients, the prevalence of DM was 32.3%. Of the patient group, 22.5% had diet/OHA - controlled DM, and 9.7% had insulin-controlled DM (Table 6.6). Mean (SD) glucose levels among patients were 6.1 (1.3) mmol/L. Using ANOVA and *post-hoc* Tukey analysis, those without DM had significantly lower serum glucose levels than those with diet/OHA-controlled DM (P = 0.001), but not those with insulin-controlled DM. Similarly, HbA_{1c} among non-diabetics was statistically lower than those with diet/OHA-controlled DM, but not insulin-controlled DM. For controls, there was no difference between non-diabetics and diabetics for either HbA_{1c} or serum glucose. When comparing levels between chronic pancreatitis patients and controls, patients had significantly higher HbA_{1c} levels than controls (P = 0.009, Figure 6.5), but not glucose (P = 0.341). Serum glucose and HbA_{1c} levels were strongly correlated for both patients (R = 0.828, P <0.0001) and controls (R = 0.845, P <

0.0001). Chronic pancreatitis patients were significantly more likely to take PERT if they also had DM (P = 0.046, Table 6.7). There were no statistical relationships between the occurrence of DM and alcohol aetiology, pain score, years since diagnosis, or the presence of pancreatic calcifications.

Table 6.5 Mean faecal elastase-1 values for disease severity, pain, DM, and vitamin deficiency

		n	Faecal elastase-1 mean (SD)	95% CI	*P*
Disease severity	Mild/moderate	32	379 (182)		
	Severe	13	135 (161.5)	(-332.3, -97.2)	0.001$^{\mu}$*
	No pain	25	351 (194)		
Pain score	Pain score >1	21	269 (212)	(-39.2, 203)	0.18$^{\mu}$
	Yes	20	299 (209)		
DM	No	26	334 (203)	(-87.0, 155.9)	0.57$^{\mu}$
Vitamin A	Deficient	8	210 (202)		
	Not deficient	32	352 (197)	(318.4, 35.2)	0.1$^{\mu}$
Vitamin E:Lipid	Deficient	12	267 (187)		
	Not deficient	29	353 (207)	(-222.9, 51.6)	0.21$^{\mu}$
Vitamin D	<25 nmol/L	5	317 (126)		
	>25 nmol/L	41	314 (213)	(-151.6, 157.4)	0.97$^{\mu}$

*Achieved statistical significance, μ Student's t-test (comparing mean levels of faecal elastase-1 for each group)

Table 6.6 Prevalence of DM, and a comparison of HbA_{1c} and glucose between chronic pancreatitis patients and controls

	Chronic pancreatitis			Controls			
Prevalence	Non-diabetic	42 (67.7)		Non-diabetic	62 (94)		
	Diabetic	20 (32.3)		Diabetic	2 (3)		
	Insulin-controlled	6 (9.7)		Insulin-controlled	0		
	OHA/diet-controlled	14 (22.5)		OHA/diet-controlled	2 (3)		
	New diagnosis	0		New diagnosis	2 (3)		
HbA_{1c} (%) mean (SD)	All patients	6.1 (1.3)		All patients	5.5 (0.9)		
	Non-diabetic	5.3 (1.1)		Non-diabetic	5.5 (1.0)		$P = 0.009^{*\,\mu}$
	Insulin-controlled	6.5 (1.3)	$P = 0.001^{*\,\S}$	Insulin-controlled	-	$P = 0.22^{\beta}$	95% CI (-0.9, -0.1)
	OHA/diet-controlled	7.2 (2.1)		OHA/diet-controlled	7.1 (0.8)		
Glucose (mmol/L)	All patients	6.6 (3.2)		All patients	6.1 (2.3)		
	Non-diabetic	5.5 (1.1)		Non-diabetic	6.0 (2.3)		$P = 0.341^{\mu}$
	Insulin-controlled	8.5 (5.8)	$P = 0.001^{*\#}$	Insulin-controlled	-	$P = 0.31^{\beta}$	95% CI (-1.5, 0.5)
	OHA/diet-controlled	8.8 (4.2)		OHA/diet-controlled	9.1 (2.3)		

* Achieved statistical significance

§ ANOVA comparison of HbA_{1c} within chronic pancreatitis group, significant difference between non-diabetic and OHA/diet controlled diabetic only (Tukey *post-hoc* analysis)

ANOVA comparison of glucose within chronic pancreatitis group, significant difference between non-diabetic and OHA/diet controlled diabetic only (Tukey *post-hoc* analysis)

β Student's T-test comparing non-diabetic and OHA/diet groups within control group

μ Student's T-test comparing HbA_{1c} / glucose levels between chronic pancreatitis and control groups

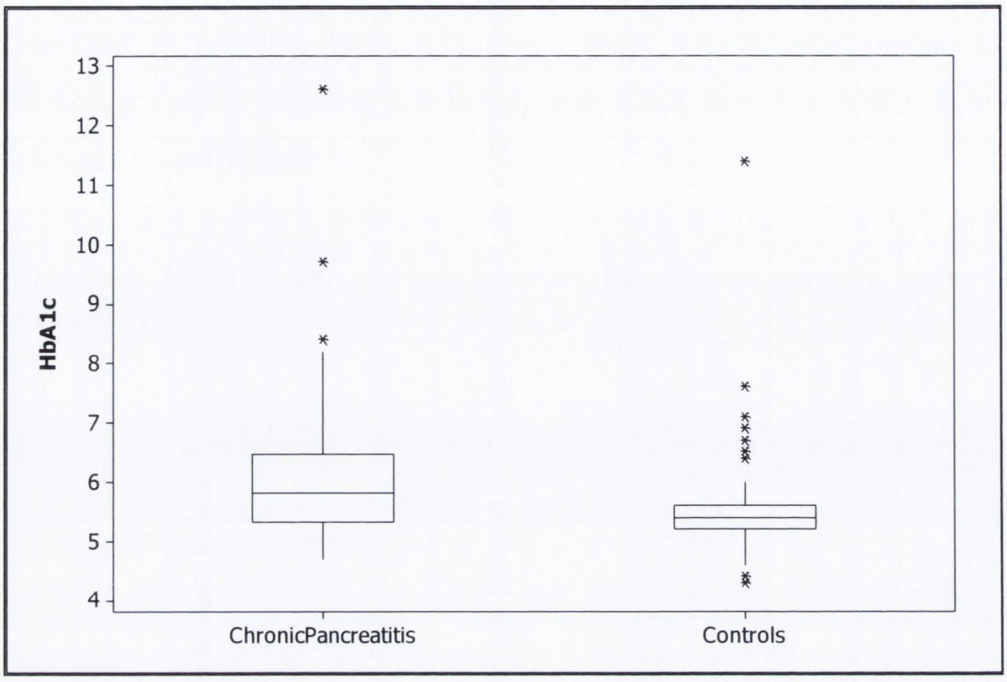


Figure 6.5 Mean HbA_{1c} of controls compared to patients

95% CI for difference: (-0.9, -0.1), $P = 0.009$

Table 6.7 Patients taking PERT are more likely to also have pancreatogenic DM

	Not taking PERT	Taking PERT	
Not Diabetic	24	18	
Diabetic	6	14	$P = 0.043$

Pearson's χ^2 test = 3.997

6.3.7 Adverse symptoms and pain

Table 6.8 details the most common symptoms reported by patients on the day of assessment. The most common was 'intermittent or occasional pain' (69.4%), followed by 'malabsorption' (61.7%) and 'anorexia/ early satiety' (45%). Almost half (43.5%, n = 27) of patients reported pain on the day of assessment. The mean (SD) pain score reported among all patients was 1.55(2.2). Of those reporting any pain on the day of assessment, the mean (SD) score was 3.6 (1.9), with seven patients (11.3%) reporting pain of $\geq$5. When asked to describe the nature of their pain, 30.6% (n = 19) of patients described it as '*constant*', with 69.4% (n = 43) describing it as '*occasional*'. Those with constant pain were more likely to also report 'malabsorption' (P = 0.006) and vomiting (P = 0.015) as common symptoms (Table 6.9).

6.3.8 Supplement usage

Supplement use of patients and controls are detailed in Table 6.10. The most commonly used supplements among patients were ONS and multivitamins, followed by iron and calcium/vitamin D. Among controls, over a third (37.9%) reported taking multivitamin preparations, with omega-3/ fish oils being the next most commonly used (19.7%). No patients were taking antioxidant preparations specifically intended for relief of pain (such as *Antox*®), nor had any patients taken such a preparation in the past.

6.3.9 Social factors

6.3.9.1 Hospital admissions

Half of patients had at least one hospital admission in the year prior to assessment (Table 6.11). More than 8% had at least 3 admissions. In contrast, the majority of controls (94%) did not have any hospital admissions in the year before study participation. The total bed days in Tallaght Hospital for chronic pancreatitis patients in the year preceding assessment was 831 days. This is equivalent to 2.28 full-time beds in this institution for a full year. The difference between total hospital admission days for patients and controls was highly significant (P < 0.001).

6.3.9.2 Alcohol & smoking

The number of patients and controls who were 'never' drinkers were statistically similar (Table 6.11). However, while almost half of patients were ex-drinkers (46.8%), only 3% of controls fell into that category. The vast majority of controls were current drinkers, and despite their disease, almost half of patients continued to drink. There appeared to be no relationship between pain type and categories of alcohol intake. More than half the patient group (59.7%) were 'current' smokers. And just one quarter (25.8%) were 'never' smokers. Smoking was higher among patients than controls, despite matching of the subject groups by education level. Patients were also significantly heavier smokers than controls in terms of pack years ($P = 0.028$).

6.3.10.3 Employment

A third of patients (35.5%) reported being out of work as a direct consequence of chronic pancreatitis, and just over half were working in either full- or part-time jobs. These data were statistically different from the control group, among which 97% were in either full- or part-time employment (Table 6.11).

Table 6.8 Symptoms reported by patients with chronic pancreatitis from a pre-defined list

Symptom	n	%
Intermittent/ occasional pain	41	66.1
Malabsorption	37	61.7
Anorexia/ satiety	27	45.0
Vomiting	22	36.7
Daily/ constant pain	21	33.9
Fatigue	13	21.0
Taste disturbances	10	16.7
Constipation	9	14.5
Bloating	8	12.9
Acid reflux	4	6.4

Table 6.9 Symptoms according to type of pain reported

		Intermittent pain pattern	Constant pain pattern	*P*
Number (%)		41 (66.1)	21 (33.9)	
Sex	Male	29 (46.8)	16 (25.8)	NS[§]
	Female	12 (19.3)	5 (8.1)	
Age, mean (SD)		47.9 (12.4)	48.1 (13.1)	NS[β]
BMI, mean (SD)		25.6 (4.8)	26.1 (5.5)	NS[β]
Regular analgesia	Yes	22 (35.5)	18 (29.0)	0.003[§]*
	No	19 (30.6)	3 (4.8)	
PERT (per Kg), mean (SD)		367 (528)	713 (637)	0.039*
Pain score, mean (SD)		0.6 (1.6)	3.4 (2)	<0.001[β]*
Malabsorption	Yes	19 (30.6)	18 (29)	0.003[§]*
	No	22 (35.5)	3 (4.8)	
Vomiting	Yes	11 (17.7)	11 (17.7)	0.047[§]*
	No	30 (48.4)	10 (16.1)	
Poor appetite	Yes	15 (24.2)	10 (16.1)	NS[§]
	No	26 (41.9)	11 (17.7)	
Not working due to illness	Yes	16 (25.8)	6 (9.7)	NS[§]
	No	25 (40.3)	15 (24.2)	
Smoking, pack years		16.1 (17.8)	25.2 (29.4)	NS[β]
Alcohol	Never/ex	20 (32.3)	13 (20.9)	NS[§]
	Current	21 (33.9)	8 (12.9)	
Faecal elastase-1, mean (SD)		340 (197)	266 (216)	NS[β]

* Statistically significant, § Chi-square, β Student's t-test

Table 6.10 Nutritional supplement usage among patients and controls

	Patients n (%)	Controls n (%)
ONS (sip feeds)	11 (17.7)	0
Multi vitamin/mineral	11 (17.7)	25 (37.9)
Iron	8 (12.9)	2 (3)
Calcium/ vitamin D	6 (9.7)	4 (6.1)
Omega-3, fish oil	5 (8.6)	13 (19.7)
Garlic	2 (3.2)	2 (3)
Vitamin C	1 (1.6)	2 (3)
Glucosamine	1 (1.6)	7 (10.6)
Ginseng	1 (1.6)	1 (1.5)
Thiamin	1 (1.6)	0
Vitamin B12	1 (1.6)	0
B-complex	0	3 (4.5)
Antioxidants	0	1 (1.5)
Evening primrose oil	0	1 (1.5)
Folic acid	0	1 (1.5)
Magnesium	0	1 (1.5)
Protein	0	1 (1.5)
Probiotics	0	1 (1.5)
Gluteine	0	1 (1.5)
Calcium	0	1 (1.5)

Table 6.11 Social factors among patients and controls

		Chronic pancreatitis	Controls	*P*
Admissions to hospital	None	31 (50.0)	62 (93.9)	
	1-2	26 (41.9)	4 (6.1)	
	≥3	5 (8.1)	0	
	Median (IQR) admissions	0.5 (1,7)	0	
	Median (IQR) LOS	15 (8, 48)	5 (1, 6)	
	Mean (SD) LOS	27.3 (29.7)	4 (2.6)	<0.001*$^{\mu}$
	Total bed days for all subjects	831	12	
Alcohol, n (%)	Never drinker	4 (6.4)	4 (6.1)	
	Ex-drinker	29 (46.8)	2 (3)	
	Current drinker	29 (46.8)	60 (90.9)	
	Units per week	22.4 (31.3)	14.7 (10.6)	0.25$^{\mu}$
	Range	1-112	1-59	
Smoking, n (%)	Never	16 (25.8)	26 (39.4)	
	Ex-smoker	9 (14.5)	21 (3.0)	
	Current smoker	37 (59.7)	19 (26.2)	
	Mean pack years	26 (22.5)	16.5 (17.2)	0.028*$^{\mu}$
Employment status	Full-time employment	26 (41.9)	58 (87.9)	
	Part-time employment	8 (12.9)	6 (9.09)	
	Retired due to age	2 (3.2)	1 (1.5)	<0.001*§
	Retired due to illness	22 (35.5)	0	
	Unemployed (social reasons)	4 (6.4)	1 (1.5)	

* Statistically significant, μStudent's t-test, § Pearson's χ^2 test

IQR Interquartile range

6.4 Discussion

6.4.1 Demographics, nutritional status and anthropometry

The most common form of 'malnutrition' in this study was excess body weight; half of patients with chronic pancreatitis were overweight or obese. Only ten percent were clinically underweight. A few studies have reported BMI in chronic pancreatitis, most in the context of other investigations. At 25.9 Kg/M^2 for males and 25.5 Kg/M^2 for females, the BMI of this Irish group was higher than in other reported studies: 19.3 Kg/M^2 (India)[95]; 21.9 Kg/M^2 (Italy)[97]; 22.1 Kg/M^2 (Poland)[189]; 23 Kg/M^2 (Denmark)[94]; 24 Kg/M^2 (The Netherlands)[191]; and 24.3/24.9 Kg/M^2 (male/female, personal communication from *D. Yadav of the NAPS2 Consortium, USA*). Of these studies, the latter two (with the highest BMIs) are the most recently-published, and therefore it may be that a higher BMI among chronic pancreatitis patients is reflective of ever-increasing obesity in society.

Nevertheless, despite obesity among patients, they still appear to have a lower BMI than among the general population. Only the Indian and Italian studies recruited a comparative control arm, and they found significantly higher BMIs in controls compared to patients, which was consistent with findings in the current study. The clinical consequence of obesity in chronic pancreatitis is uncertain. However, the presence of obesity may mask malnutrition, muscle depletion (sarcopenia), and vitamin deficiency. Ammann *et al* reported that obesity may be a risk factor for the development of co-morbid disease, inflammation and alcoholic chronic pancreatitis[192].

Despite the prevalence of obesity among patients, the data showed that muscle mass and functional capacity were lower in patients than in controls. Few studies have examined muscle and fat stores in chronic pancreatitis. One study of 120 patients from India with idiopathic chronic pancreaitis[45], BMI, muscle and fat stores (including MUAC, TSF) were all significantly lower in patients compared to controls. In a second study from India[95], the BMI, fat stores and muscle stores of patients with alcoholic chronic pancreatitis and tropical chronic pancreatitis were significantly lower than that of controls (but were not different between aetiologies). However direct comparisons with the current study are unwise, as the

aetiology and ethnicity of patients from India are so vastly different from those of Western populations. In the current study, handgrip strength was lower among older patients, which is not unexpected. Handgrip strength was also lower among patients who were 'weight-losing', which may indicate its use as a marker of deteriorating nutritional status in chronic pancreatitis. In a study on Crohn's Disease patients in remission, Bin *et al*[193], found that handgrip strength was more sensitive than other methods for detecting clinical malnutrition. Handgrip strength as a marker of functional capacity has been linked to nutritional status in renal[194] and surgical patient groups[195], and to prognostic factors in a renal population[194].

6.4.1.1 CT-based measurement of muscle mass

While MUAC and TSF are validated methods of measuring muscle and fat stores, there are inherent limitations with accuracy and reproducibility. Similarly, BMI, though widely used, does not discern between muscle and fat and is a crude measure of body weight. A more accurate method of body composition analysis involves the use of CT images. Muscle mass is measurable by secondary analysis of previously analysed CT images, taken for diagnostic purposes.[196] Investigation of the relationship between sarcopenia (depletion of skeletal muscle) and clinical outcomes (including severity, mortality, and QOL) in chronic pancreatitis are warranted, and this area of nutritional analysis has not previously been applied to this patient group. In particular, the prevalence of sarcopenic obesity should be investigated, where obesity and low muscle mass occur simultaneously combining the health risks of obesity and depleted lean mass[196]. Given the high prevalence of obesity in the current study along with a demonstrably low muscle mass and strength compared to controls, CT-based body composition analysis would complement work done to date.

6.4.1.2 Albumin and nutritional status

Albumin is more suited as a marker of morbidity than of nutritional status, due to its association with CRP and the fact that it is affected by non-nutritional factors, including liver and renal function[197]. The data from the present study showed a moderate negative correlation between albumin and CRP ('sicker' patients had the lowest serum albumin). In

addition, albumin was lowest in the most severe grades of chronic pancreatitis and in the most underweight patients. Patients with the lowest albumin levels also had the lowest serum fat-soluble vitamin levels, and the relationship between albumin and vitamins E and A were independent of inflammation. Serum albumin levels were within the normal reference range, and therefore the clinical application of these findings is unclear. However, these data suggest that albumin may be a viable biochemical marker of malnutrition in patients with chronic pancreatitis.

6.4.2 Vitamin status

6.4.2.1 Vitamin deficiency in chronic pancreatitis patients

Vitamin A deficiency occurred more in patients (16%) than in controls, but was less prevalent than reported in older studies[103], and considerably higher than data from a recent uncontrolled Dutch study on 44 chronic pancreatitis patients (3%)[191]. Vitamin A deficiency was more common among patients of lower BMI and in those with alcohol-induced pancreatitis. Consistent with previous reports[100-101, 191] vitamin E deficiency was more common than that of vitamin A. Vitamin E deficiency was more prevalent when correctly expressed as a ratio of blood lipid (vitamin E is bound to lipid in the serum). Most common of all was vitamin D insufficiency[198], but this is unlikely to be solely a manifestation of chronic pancreatitis, and in fact, the levels were not different on average than for controls. This is likely to reflect the public health problem of vitamin D inadequacy, particularly in countries of northern latitude such as Ireland. Patients with chronic pancreatitis are likely to benefit from vitamin D supplementation. A recent study showed that daily vitamin D supplement of 1520 IU increased 25-OH D in patients with chronic pancreatitis compared to a placebo[199].

6.4.2.2 Hypervitaminosis in chronic pancreatitis patients

While we set out to determine the occurrence of vitamin deficiency among patients, we did not expect to encounter hypervitaminosis. A perplexing finding was that more patients had vitamin A excess than vitamin A deficiency. Predisposing liver disease may greatly increase susceptibility to vitamin A excess and lower the amount of vitamin A needed for adverse

affects to well-below the threshold for normal persons[200]. However, none of the vitamin A excess group had liver dysfunction as measured by liver function tests. Alcoholism and protein-energy malnutrition may also enhance susceptibility to vitamin A toxicity[200]. However, only 2 of the 12 patients had alcohol-related chronic pancreatitis, and none were underweight. Vitamin A toxicity may occur following mega doses of supplements over years[200]; however this group were not taking high-dose vitamin A supplements. Two of the twelve patients were taking low dose supplements (multivitamins) at the time of assessment, the rest were not. Although dietary intake assessment was not among the study's objectives, upon diagnosis with hypervitaminosis, patients were telephoned as a follow-up. Each confirmed that they were not taking vitamin A containing supplements (other than multivitamins) and none had abnormally-high intakes of vitamin A-rich foods. Those with vitamin A excess had higher vitamin E levels on average, which could suggest that toxicity of these vitamins may occur simultaneously. A literature search yielded no previous reports of hypervitaminosis A in chronic pancreatitis, and the significance of the finding is unclear. Unlike seen with vitamin A, almost equal number of patients and controls had vitamin E excess, although this number was lower in both groups when vitamin E was expressed as a ratio of lipid. Hypervitaminosis E (unlike that of vitamin A) is likely to be reflective of dyslipidaemia, as vitamin E is bound to lipid in the serum.

6.4.2.3 Prior reports of clinical nutrient deficiency

6.4.2.3.1 Vitamin E

While several studies have reported variable prevalence of subclinical vitamin E deficiency in chronic pancreatitis, the clinical importance of biochemical vitamin E deficiency is not clear. Many of the studies reporting overt clinical manifestations of nutrient deficiency in chronic pancreatitis are isolated case-reports. One such case report[201] described a patient with chronic calcific pancreatitis and coeliac disease, who presented with adenocarcinoma of the colon. The authors made an association between vitamin E deficiency and the development of colorectal cancer, hypothesising that vitamin E deficiency due to malabsorption in these conditions may contribute to the high incidence of GI cancer in both chronic pancreatitis and

coeliac disease. The patient developed a condition known as brown bowel syndrome, a rare disorder characterised by a brown pigmentation of the bowel wall. This syndrome has been described in a variety of malabsorption syndromes and is specifically associated with vitamin E deficiency[201]. While the exact pathway is not known, it is thought that vitamin E protects the mitochondrial membrane from damage by free radicals. In vitamin E deficiency the free radicals are not oxidised by vitamin E, but by the phospholipids of the mitochondrial membrane, which degradate. The result is formation of lipofuscin in the tunica muscularis causing a brown colour[201]. While brown bowel syndrome is a rarely reported condition, the typical manifestations of vitamin E deficiency are neurological in nature: peripheral neuropathy, ataxia, weakness, spinocerebellar disease and hyporeflexia, as well as non-neurological symptoms (cardiac arrhythmia, blindness, haemolytic anaemia, and dementia)[202]. However, in a case-series of 13 patients with documented vitamin E deficiency due to acquired fat malabsorption, only one patient had typical neurological manifestations of vitamin E deficiency[102]. The patient had poorly-controlled DM due to advancing chronic pancreatitis. The authors suggested that patients with DM tend to have early neurological deficiency symptoms.

6.4.2.3.2 Vitamin A

Clinical deficiency of vitamin A tends to manifest as visual defects. On the ocular surface, vitamin A is necessary for epithelial cell RNA and glycoprotein synthesis. As a result, vitamin A deficiency has a wide range of ocular manifestations including conjunctival and corneal xerosis, keratomalacia, retinopathy, visual loss, and nyctalopia (night blindness), which is the earliest and most common symptom[203]. Non-visual effects include problems with growth and susceptibility to infection. As is the case for vitamin E, reports of vitamin A deficiency in chronic pancreatitis are confined to case-reports. One such case-report from Spain published in 2005 reported the case of a 45-year old male with chronic pancreatitis associated with a history of chronic alcoholism, DM and cholecystectomy[173]. The patient presented with steatorrhoea, cachexia, low BMI and severe weight loss along with bilateral ocular pain, photophobia and decreased visual acuity. Vitamins A, D and E were biochemically low and the patient was anaemic. Therapy included diet, PERT, insulin, and vitamin supplementation,

with correction of the visual deficits and malnutrition within a period of 4 months[173]. In the same year, a second Spanish case-report was published (in Spanish and available in abstract form only, the authors were not contactable) detailing the case of a patient with alcoholic chronic pancreatitis with malnutrition and vitamin A deficiency. The patient developed peripheral ulcerative keratitis in one eye and necrotising stromal ulceration with hyphema in the other eye.

6.4.2.3.3. Vitamin D

While mild vitamin D deficiency (insufficiency) is thought to affect several body systems, the condition most associated with severe vitamin D deficiency is osteomalacia (equivalent to childhood rickets). Osteomalacia is failure to mineralise newly-form osteoid in bone, resulting in a softening of bone, pain and weakness. It occurs due to a reduction in the absorption of dietary calcium from the intestines as a consequence of vitamin D deficiency. Reports of osteomalacia due to vitamin D deficiency in chronic pancreatitis are also confined to case-reports. One such report described a 30 year old woman who was confined to a wheelchair due to severe myopathy. She had a history of steatorrhoea since childhood for which she had a restrictive vegetarian diet. Upon assessment, she was underweight, and had low serum calcium, phosphate and albumin, as well as low serum 25-OH D. Serum levels of vitamin B12 and vitamin A were also low. A diagnosis of osteomalacia was made and therapy included vitamin D, calcium supplementation and PERT which resulted in improvements in muscle pain and strength and a subsequent full recovery of mobility[204]. A second case-report described a 22 year old woman with chronic pancreatitis and a history of pancreatico-jejunostomy. She presented four years after surgery with steatorrhoea and osteomalacia. She was also successfully treated with vitamin D, calcium and PERT[205]. A third case-report details a patient with chronic pancreatitis and DM who had a pancreaticoduodenectomy due to a suspect mass at the head of the pancreas. Eight years later he presented with decreased muscle power, arthralgia of the hip, foot and knees, along with low serum vitamin D levels. When treated with vitamin D, supplementary PN and PERT, his symptoms resolved within 2 weeks[206].

6.4.2.3.4 Deficiencies of other vitamins

Deficiencies of vitamin B12 and folate do not appear to be common in chronic pancreatitis. In 137 chronic pancreatitis patients, vitamin B12 and folate levels were measured. Seven patients (5.7%) had B12 deficiency, with no correlation to disease severity. Five patients (3.6%) had low folate levels[105].

6.4.2.3.5 Trace-element deficiency in chronic pancreatitis

Trace-element status was not measured in the current study. Biochemical zinc deficiency has been previously reported in chronic pancreatitis compared to controls, particularly in those with tropical pancreatitis compared to alcohol-induced pancreatitis. Zinc levels correlated with both exocrine and endocrine insufficiency. None of the patients had any overt clinical signs that suggested zinc deficiency[207]. A study of 13 patients with chronic pancreatitis and 8 controls investigated magnesium deficiency. As serum magnesium is a poor indicator of deficiency, the retention of a low-dose intra-venous magnesium load was determined. Ten of the 13 patients showed evidence of magnesium deficiency[208].

In general, reports of overt symptoms of deficiency associated with chronic pancreatitis are rare. Despite the high prevalence of biochemical deficiency reported for some vitamins, there do not appear to be many reports of clinical manifestations. It may be that isolated cases of deficiency go unreported, or alternatively, it may be that the effects of subclinical nutrient deficiency are subtle and rarely obvious. In most reported cases, overt deficiency symptoms occurred when there was an additional condition or morbidity (as well as chronic pancreatitis), such as DM[102, 173, 206], coeliac disease[201], or GI surgery[205-206]. It also appears that clinical deficiencies take years to develop[204-206]. Table 6.12 summarises the current literature on nutrient deficiency in chronic pancreatitis.

Table 6.12 Reports of biochemical and clinical nutrient deficiencies in chronic pancreatitis

Nutrient	Reports of biochemical deficiency	Reports of clinical deficiency
Vitamin A (retinol)	16% prevalence (South Africa)[103] §40% prevalence (Japan)[101] **14.5% prevalence (Ireland, current study)** 3% prevalence (The Netherlands)[191]	Bilateral ocular pain, photophobia, decreased visual acuity[173] Peripheral ulcerative keratitis Necrotising stromal ulceration with hyphema[209]
Vitamin E	75% prevalence (South Africa)[100] 75% prevalence (South Africa)[103] §30% prevalence (Japan)[101] **24.2% prevalence (Ireland, current study)** 10% prevalence (The Netherlands)[191]	Brown bowel syndrome[201] Neurological manifestations[102]
Vitamin D	α 13.6% prevalence (Czech Republic) **α 11.2% prevalence (Ireland, current study)** α 58.3% prevalence (Argentina) #53% prevalence (The Netherlands)[191] β 86% prevalence (India)[210] §16.7% prevalence (Japan)[101]	Osteomalacia[204-206]
Vitamin B12	5.7% prevalence (Germany)[105]	
Folate	3.6% prevalence (Germany)[105]	
Magnesium	77% prevalence (UK)[208]	
Zinc	Lower zinc in patients than controls, and lowest in tropical chronic pancreatitis (India)[207]	

§ Deficiency defined as less than 2 SD below levels of normal controls, α Deficiency <25 nmol/L, # Deficiency <38 nmol/L , β Deficiency <50 nmol/L, tropical pancreatitis

6.4.3 Exocrine function

While there was an association between disease severity and PEI, there was no statistical association between PEI and endocrine dysfunction or deficiencies of the measured vitamins. However, only 46 of 62 patients opted to provide a faecal sample for assessment thus reducing the statistical power to detect differences if they exist. Moreover, the lack of correlation between vitamin levels and faecal elastase-1 may be due to the fact that some patients had excess vitamin levels. Only a third of the group had low faecal elastase-1, although notably 61.7% reported malabsorptive symptoms. As more than half were taking PERT, it appears that practice appears to be veering towards over-, rather than under-treating with PERT. In contrast, *Sikkens et al* found that 70% of their patients were exocrine insufficient, but less than half were in receipt of PERT. Neverthless, PERT *dosage* was low in the present study. Considering that the maximum recommended dosage for PERT is 10,000 U lipase per Kg body weight[177], the highest user of PERT in the current study took just over 2,000 U lipase/Kg, which is considerably below the maximum. The mean usage was very conservative (less than 1,000 U lipase / Kg). Given the proportion of patients that reported malabsorption, the significantly lower anthropometric indices, and the higher proportion of fat-soluble vitamin deficiency among patients, practice regarding PERT requires considerable improvement.

6.4.3.1 Treatment with PERT in chronic pancreatitis

Success with PERT in chronic pancreatitis relies on appropriate prescription, adequate dosage, meticulous follow-up and detailed patient education. Therefore, the development of treatment algorithms for PERT administration is vital. Several such guidelines have been published to date[211-213]. Many of the current guidelines for PERT recommend a starting dose of 40,000-50,000 U lipase per meal[115, 212], doubling the dose[212] and increasing to a maximum of 10,000 U lipase per Kg[177] if treatment is ineffective. The most recent trials on the effectiveness of PERT in increasing fat and nitrogen absorption used doses of up to 80,000 U lipase per meal[214-215] (which is twice the dose given per meal in older studies[170, 181]). PERT is a safe[214-215] and cost-effective[216] therapy for PEI in chronic pancreatitis. A clinical management

framework for PERT administration developed for use in Tallaght Hospital is provided in Chapter 9.

6.4.4 Endocrine function

6.4.4.1 The prevalence and nature of type 3 DM in chronic pancreatitis

The prevalence of DM from the current study was almost 1 in 3 (32.3%), which was largely consistent with previous international studies. Although not usually referred to as such, the prevalence of type 3 DM in chronic pancreatitis varies between countries and has been reported as 5% (Australia), 21.6% (China)[217], 32% (France)[218], 35% (Poland)[189], and 39.7% (Japan)[39]. Rates of DM in India tend to be higher, with 39%[219] - 55%[41] being reported, probably attributable in many cases to aetiology (tropical pancreatitis), although the high incidence reported by Garg *et al*[41] may have been due to bias in recruitment from DM clinics. The current study represents the first study of DM prevalence in an Irish or UK chronic pancreatitis population, and is among the first in Europe.

6.4.4.2 Type 3 DM

Type 3 (or type 3c DM) was classified as a type of DM by the American Diabetes Association[220]. It is associated with benign and malignant diseases of the pancreas, including acute and chronic pancreatitis, pancreatic neoplasms, pancreatic trauma, pancreatic resection, cystic fibrosis, haemochromatosis, fibrocalculous pancreatopathy and pancreatic agenesis[92, 220]. Chronic pancreatitis patients make up the bulk of patients with this DM subtype (> 75%)[90]. Patients with type 3 DM are frequently misclassified as type 1 or 2, despite having substantial differences in clinical and biochemical features compared to types 1 and 2[90]. Incorrect diagnosis of those with type 3 DM may lead to a failure in the application of appropriate medical therapy. This deficit in management may be perpetuated by a failure by the American Diabetes Association (and others) to include type 3 DM in its guidelines for therapy[91]. In fact, compared to data on the prevalence of types 1 and 2 DM, data on type 3 DM hardly exists. One study from Germany by Ewald and colleagues retrospectively re-analysed the cases of 1,868 patients with a diagnosis of DM[90]. They reported that

misclassification of type 3 diabetics was common, usually as type 2. In general, true type 3 patients tended to be older than type 1 patients but younger than type 2 patients. Most of the true type 3 cases had chronic pancreatitis, and most were men (possibly due to the fact that chronic pancreatitis is more common in men).Type 3 DM patients had significantly higher BMI than type 1 patients, but lower than type 2 patients. Contrary to the belief that type 3 DM patients have poorer glycaemic control, HbA_{1c} did not differ between the 3 subgroups[90]. In the current study, HbA_{1c} was higher among patients (both diabetics and non-diabetics) than in the control group. However, there was no difference in glucose levels. Among chronic pancreatitis patients, HbA_{1c} for non-diabetic patients (5.3%) was similar to the level for the control group (5.5%). The HbA_{1c} of patients on insulin (6.5%) was more favourable on average than the levels for those controlled with diet and / OHAs (7.2%). This may reflect the occurrence of frequent episodes of hypoglycaemia for those on insulin therapy, although this was not measured. It might also be a reflection of poorer glycaemic control for those on diet/OHA treatment only.

6.4.4.3 Suggested principles of management and strategies for treatment of type 3 DM in chronic pancreatitis

In the last 2-3 years, several authors have highlighted type 3 DM as a distinct entity, which requires more research, clinical awareness, and the development of management guidelines. In a review on the topic in 2011, Cui & Andersen provided some direction on the provision (or avoidance) of insulin, and the administration of metformin therapy[92]. Regarding lifestyle modification, little guidance was provided beyond the avoidance of factors that contribute to hyperglycaemia and the risk of malignancy. Specifically, weight loss in the obese patient, daily exercise, limited carbohydrates, and alcohol/smoking cessation were specified as critical elements for discussion at the patient consult. The role of PERT was highlighted as a key factor in management of patients with pancreatic disease[92]. The dietary management of patients with chronic pancreatitis-related type 3 DM is complicated for several reasons. Progressive loss of insulin results in hyperglycaemia, which may be exacerbated by a diet unusually high in carbohydrate due to the tendency (often unnecessary and ill-advised) to avoid fat. Concurrent destruction of the glucagon-producing cells renders the patient

susceptible to episodes of hypoglycaemia. This process is exacerbated by poor or erratic eating patterns and malabsorption of food. Furthermore, over-treatment or inappropriate dosage of insulin may augment the problem. For these combined reasons, the patient with chronic pancreatitis tends to be a difficult patient in terms of dietary management. While the management of DM cannot be separated from the overall dietary management of chronic pancreatitis, there are several key principles that may improve treatment and reduce the likelihood of dangerous swings in glycaemic control. Taking prevention of hyperglycaemia, hypoglycaemia, malnutrition and the co-morbidities associated with DM as the main principles of management, the following strategies should be employed. Meals should not be skipped, and should be small, frequent, and taken at regular time intervals to aid glycaemic control. Appropriate and adequate PERT should be administered to minimise malabsorption. Frequent measurement of glucose levels should be encouraged to determine adequacy of DM control, and to pre-empt hypoglycaemic events. Special attention should be given to glucose measurement when dietary intake is poor or after physical activity, particularly where this deviates from the normal routine. By minimising high sugar / high glycaemic index food, spikes in blood glucose may be avoided. The recording of diet, glucose levels, PERT, and exercise will help to identify difficult areas of control. Finally, given the complex nature of the dietary management of DM in chronic pancreatitis - and given that the patient also must contend with PERT, nutrient deficiency, bone health and adverse symptoms - regular assessment and support by a pancreatic dietitian is crucial. Table 6.13 summarises the suggested strategies for the nutritional management of type 3 DM in chronic pancreatitis.

Table 6.13 Suggested principles of nutritional management, and management strategies for type 3 DM in chronic pancreatitis

Principles of management	Management strategies
Prevent: Hypoglycaemia Hyperglycaemia Exacerbation of malnutrition Co-morbidities associated with DM (e.g. retinopathy, renal disease)	Do not skip meals Take small, frequent meals Measure glucose levels frequently, particularly after physical activity, and if diet is poor Avoid alcohol Ensure adequacy of PERT Minimise high-sugar/ high-glycaemic index food or fluids Consider a diary to record diet, blood glucose levels, PERT, exercise - at least until acceptable blood glucose control is maintained Dietitian assessment/ monitoring

6.4.5 Adverse symptoms and pain

The NAPS-2 consortium[184] in a 2011 publication (based on the AGA technical review on the topic[187]) suggested that pain in chronic pancreatitis be divided into 5 categories according to the *frequency* and *severity* of pain. As the current study preceded the NAPS-2 publication, the above classification could not be ascertained in retrospect. However, data were available on the frequency of pain (termed 'constant' or 'occasional' in the current study) and therefore, comparisons can be drawn between this study and the 2011 paper by the NAPS-2 consortium who termed pain as 'constant' or 'intermittent'. The authors suggested that classification of pain by frequency was more useful than classification by severity. There were notable differences between the study groups in the current study and the NAPS-2 study. The NAPS-2 study was a multicentre prospective study involving 20 centres in the US which included 540 chronic pancreatitis patients, and therefore was considerably larger in scope and power than the current study. The NAPS-2 study found that those with constant pain were more likely (than those with intermittent pain) to be younger, be heavier drinkers, heavier smokers, use regular analgesia and be 'disabled'. Although it is likely that the current study was underpowered to detect differences within subgroups of pain, particularly given that the number of patients reporting constant pain was low (n = 21), there did appear to a noteworthy relationship with pain frequency for some indices. Patients in the current study were marginally younger than the NAPS-2 group (by 1 year on average), less likely to abstain from alcohol (6.5% 'never' drinkers compared to 23% 'abstainers' in NAPS-2), heavier smokers (59.7% current smokers compared to 47.6% in NAPS-2) and more likely to be men (72.6% compared to 49.5% in NAPS-2). However, the data showed that those with constant pain were more likely (than those with intermittent pain) to report regular malabsorption and vomiting, take regular analgesia, take more PERT, and have more severe pain on the day of assessment (Table 6.9). There were no differences between the patterns of pain for sex, age, BMI, faecal elastsae-1 levels, smoking, alcohol, appetite, or the likelihood of not working due to illness; moreover those with intermittent pain did not have worse outcomes for any clinical features. Therefore the current study was consistent with the NAPS-2 study in demonstrating the benefits of classifying pain by frequency.

6.4.6 Supplement usage

No prior studies have examined nutritional supplement usage in patients with chronic pancreatitis in any great detail. Sikkens and colleagues in a Dutch group reported that 10% and 15% of patients were taking multivitamins and vitamin D respectively, but no other supplements were examined.[191] In the current study, a number of nutritional supplements, prescribed or otherwise, were reported by patients and controls. For patients, ONS and multivitamin / mineral supplements were the most commonly taken. Among the other supplements taken were fish oils, vitamins C, B12 and B1 (thiamin) (Table 6.10.) Antioxidant therapy was not a feature among patients, likely due to the fact that the commercially-available antioxidant preparation *Antox*® is not licenced for use in Ireland, nor have any patients taken *Antox*® in the context of clinical trials. Recent evidence[123] contradicted earlier reports of benefits[122], and therefore antioxidant therapy for pain in chronic pancreatitis remains controversial at present. Nevertheless, more research is being undertaken. The UK-based, large-scale EUROPAC2 trial (The European Registry of Hereditary Pancreatitis and Pancreatic Cancer) investigating the efficacy of antioxidants and magnesium for the treatment of chronic pancreatitis remains open for recruitment until 2015.

6.4.7 Social factors

The number of 'never' drinkers was similar for patients and controls in the current study (6.5% and 6.1% respectively). Almost half of patients reported current alcohol intake despite being diagnosed with chronic pancreatitis. This is much higher than Dutch data for current drinkers (3%)[191], but lower than data from the NAPS-2 consortium in which 63% of patients reported ongoing alcohol consumption at the time of assessment[184]. Current smoking was also prevalent among patients (59.7% compared to 26.2% of controls), and was higher than in the NAPS2 study (47.6%), but lower than among the Dutch group (68%). Therefore it seems that continental European patients with chronic pancreatitis may be smokers rather than drinkers, while USA patients and Irish patients continue to both smoke and drink in high numbers. The patients enrolled in the current study had a high hospital admission rate and, importantly, occupied more than 2 full-time beds in this institution over one year. This use of resources for such a small subset of one disease is quite remarkable, and illustrates the

resource-heavy nature of this disease. Mirroring the problem with frequent hospital admissions is the issue of employment status. More than a third of the group reported being out of employment directly due to chronic pancreatitis. As this is a cohort of young, mostly male, patients, this finding has considerable repercussions for society in general. Data on the receipt of disability benefit was not obtained in this study; however it could be assumed that those reported not working due to illness were likely to be in receipt of disability benefit. The NAPS-2 consortium found that more than 25% of their US patient group were on disability benefit. Mokrowiecka *et al*[189] reported that 24.6% of their Polish group were unemployed, although they did not specify if unemployment was due to chronic pancreatitis, or for social reasons. However, they did note that the unemployed group scored worse in many QOL indices compared to working or retired groups[189]. In the present study, there was a significant difference between patients and controls regarding marital status, with twice as many patients being single or separated/divorced/widowed (48.4%), compared to controls (22.7%). A higher QOL was previously demonstrated in married chronic pancreatitis patients[189]. In all, patients with chronic pancreatitis have considerable social obstacles which will clearly worsen their ability to cope with their progressive disease. Although it is unclear whether many of the issues are a cause or effect of disease, these factors must be borne in mind when dealing with the chronic pancreatitis patient. In addition to the debilitating physical features of the illness, patients are also more likely to drink and smoke, to have frequent hospital admissions, and are less likely to be in a relationship or in employment.

6.4.8 Study limitations

This study had a number of limitations which are listed below:

- Controls were volunteers which may have introduced bias as they may be a group who are more likely to participate in health-related surveys and studies and therefore may not be entirely representative. Nevertheless, the controls were recruited from the same geographical area as the patients and were by design closely matched for age, sex and education level.
- Recruitment of patients from tertiary referral centres introduces a bias, as this may not be representative of the typical patient with chronic pancreatitis. At present

there is no centralised model of care for pancreatitis in Ireland, and there is therefore an ad hoc element to the management of severe cases. Arguably, the care is better in tertiary centres, particularly when dealing with the consequences of disease such as nutrient deficiency.

- Some of the data recorded were dependant on patients and control self-reporting, such as whether or not they were taking vitamin supplements, and therefore an assumption is made regarding accuracy.
- Of 62 patients, 46 provided a stool sample for measurement of exocrine function. Therefore, this made subgroup analysis difficult as the power was lower than intended.
- The sample size of 62 chronic pancreatitis patients was arguably low, but this may reflect the nature of studies with this population. For example, in a systematic review of 8 trials comparing endotherapy and surgery in chronic pancreatitis, the sample sizes ranged from 39 - 74[221].
- Regarding DM, data were not recorded on the occurrence of hypoglycaemia, nor were glucagon, pancreatic polypeptide or insulin levels measured, which may have added to the recent efforts to characterise this under-studied DM subgroup.
- QOL, which is inherently linked with pain, adverse symptoms and nutritional status, was not measured.
- Body composition was done using anthropometric measures, and although these methods are validated they are also inherently limited. Analysis of visceral fat by CT would be a more accurate and useful method of assessing lean body mass.
- Analysis of dietary intake was not done, and therefore associations between diet and nutritional status were not possible.

6.4.9 Study strengths

This study's strengths were as follows:

- This study was novel in several aspects. It was the first to examine nutritional status and fat soluble vitamin deficiency in Irish patients with chronic pancreatitis, and among the first in Europe, areas of which the literature has been scarce to date.

- The study had extensive scope, covering exocrine and endocrine dysfunction, supplement use and symptoms, as well as malnutrition.
- Unlike other similar studies, including one published this year[191], the present study had a control arm allowing for direct comparisons.
- All assessments and measurements were done by a single investigator thus removing the potential for inter-observer variability.

6.4.10 Conclusions

Chronic pancreatitis is a progressive disease with debilitating symptoms including pain and malabsorption. As an incurable disease, patients require frequent hospitalisation and therefore, a good relationship between patient and clinician is imperative. In addition to the core medical/surgical team, multidisciplinary involvement is vital for the optimal management of various aspects of the disease, including pain management, nurse specialists, endocrinology, social work and nutrition. Nutritional management is vital for the management of malabsorptive symptoms, nutrient deficiencies and DM. This study has highlighted several key nutrition-related problems areas, for the first time in an Irish cohort, and among the first in the UK and Europe:

- Deficiencies of vitamins A, E and particularly D were common, although toxicity may also occur
- Patients were muscle-depleted, with poor strength, despite a high degree of overweight and obesity
- Assessment involving handgrip-strength and serum albumin may help in the identification of malnutrition
- Those with constant (*versus* intermittent) pain may have more severe features of disease
- Patients were undertreated with PERT
- A third of patients had type 3 DM, with OHA/diet-controlled patients having the most unfavourable glycaemic control

- The most common symptoms were malabsorption and pain, but anorexia, vomiting and fatigue were also common
- Nutritional supplements were taken by some, but not widely. Antioxidant therapy for pain was not used
- Many patients continued to smoke and drink despite their diagnosis

This information, when collated, gives insight into the present-day chronic pancreatitis patient, and facilitates the development of nutrition-focused management strategies within a multidisciplinary framework. In chronic pancreatitis, any additions to the knowledge-base will aid in the characterisation of the patient group, and will help to optimise management.

Chapter 7 (Part 1) details the second part of this cohort study. Specifically, it investigates the prevalence of osteoporosis and osteopenia in chronic pancreatitis.

Chapter 7 The prevalence of osteoporosis and osteopenia in chronic pancreatitis

This chapter describes a study of two parts:

Part 1 details the second phase of the cohort study described in Chapter 6 investigating the prevalence of osteoporosis and osteopenia in patients with chronic pancreatitis.

Part 2 describes a formal systematic review and meta-analysis of the data on the prevalence of osteoporosis and osteopenia in chronic pancreatitis.

7.1 General introduction

7.1.1 Normal bone

Bone is a dynamic tissue, comprising cellular, organic and inorganic components with a complex internal structure[222]. Bone is constantly being remodelled throughout life due to the activities of two major cellular elements which act in opposition: osteoclasts and osteoblasts. The activity of osteoclasts and osteoblasts are closely coupled[222]: Osteoclasts are multinucleated cells of monocyte origin which resorb bone though the release of acid and enzymes[222]. This osteoclastic phase lasts for 2-3 weeks before bone resorption ceases, presumably due to osteoclast apoptosis[223]. Osteoblasts enter the resorption pit and lay down organic matrix (osteoid) which is subsequently mineralised[222]. The osteoblastic anabolic stage is significantly longer, lasting several months. Eventually the osteoblast is buried within the newly formed bone tissue and becomes an osteocyte. The bone remodelling cycle is regulated by a myriad of factors including growth factors and cytokines[222]. This process is described in greater detail in the next chapter.

7.1.2 Low BMD

Osteoporosis is often thought of as a disease of old-age, yet it may affect individuals of any age. The WHO defined osteoporosis as a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in

bone fragility and susceptibility to fracture[128]. Osteoporosis is just one of the factors that predisposes to fracture, but it is one of the most important and can be reliably assessed by measuring BMD. Osteopenia refers to BMD that is lower than normal and could be regarded as 'pre-osteoporosis'. Together osteoporosis and osteopenia are termed 'osteopathy'. Osteomalacia is the defective mineralisation of newly formed osteoid. It is indistguishable from osteoporosis on DXA and the two conditions frequently co-exist. Clinical, radiology and biochemical findings do not reliably differentiate between them.

7.1.3 Vitamin D deficiency

Vitamin D facilitates the intestinal absorption of calcium by mediating calcium transport across the intestinal mucosa[224]. In a vitamin D deficient state (measured as 25-OH D), calcium absorption is impaired, and absorption efficacy increases as serum 25-OH D rises (up to about 80nmol/L)[224]. At suboptimal vitamin D levels, the para-thyroid glands sense calcium insufficiency and increase the secretion of PTH, thereby upregulating renal 1-α hydroxylation to physiologically appropriate levels. An increase in PTH increases bone resorption, allowing the delivery of calcium from bone, but having the effect of reducing BMD over time[224]. Therefore, adequate serum 25-OH D levels are crucial for bone health. However, dietary vitamin D is the minor source, as cutaneous irradiation (sunlight) is now recognised as the most important source of vitamin D[222]. Protracted fat malabsorption in chronic pancreatitis may contribute to vitamin D losses due to vitamin D being fat-soluble in nature.

7.1.4 Other factors that predispose to fracture

Several other factors increase the risk of fracture and are (at least partly) independent of low BMD. Non-modifiable factors include older age, prior osteoporosis fracture, family history of hip fracture, poor visual acuity and neuromuscular disorders. Modifiable factors include the use of corticosteroids, smoking and alcohol excess[110]. Regarding body weight, a low body weight of less than 40 Kg, a BMI of less than 20 Kg/M^2, or a weight loss of greater than 10% are considered high risk factors, although modifiable[110].

7.1.5 The economic burden of osteoporosis

The economic considerations are considerable. In Ireland, the direct costs associated with hip fracture alone were €35 million in 2005.[225] In the UK, there are more than 230,000 osteoporotic fractures annually costing more than £1.7 billion.[251] In the US, the National Osteoporosis Foundation estimated that in 2010, 12 million Americans of >50 years had osteoporosis or were at a significant risk of developing the disease. In 2005, osteoporosis was responsible for 2 million fractures in the US, costing more than $US 16.9 billion[226]. The WHO project that osteoporotic fractures will increase almost four-fold between 1990 and 2050[128] translating into a major drain on future healthcare resources. Crucially, osteoporosis is largely a preventable disease with appropriate screening and treatment.

7.1.6 Measurement of bone mineral density

7.1.6.1 DXA

Bone mass is the single best predictor of *in vitro* skeletal strength and fracture risk[222], and DXA is the gold standard for the measurement of bone mass[128]. DXA uses an X-ray tube to generate different X-ray energies. Bone attenuates X-rays to a larger degree than soft tissue, and lower X-ray energies are attenuated more than higher energies. The amount of attenuation for the two energies is recorded and therefore the amount of bone calcium in the path of the beam may be measured. An image of BMC (g calcium) is generated when the X-ray tube is scanned over the area of interest. Software uses an algorithm to yield BMD (g / cm^2) from BMC and bone area (cm^2)[222]. Absolute measurements of BMD are of little value, as they are determined by the site of measurement, the calibration used by the manufacturer and the particular instrument[222]. BMD deteriorates with age, therefore age-related changes need to be considered.

7.1.6.2 Z-score and T-scores

Because of machine and skeletal site differences, BMD results are noted by a derived statistical value, the T-score. Bone density measurements tend to follow a bell-shaped (Gaussian) distribution, and therefore are described as the number of standards deviations

from the mean for normal controls. Therefore, the T-score is not an absolute value, but the number of SDs above or below the BMD average value in young healthy adults[223] (which is representative of 'peak bone mass'). The Z-score is the number of SDs above or below the mean for an age-matched population[128], and is less commonly used, except in research. The WHO divided bone density into several categories: normal, osteopenia and osteoporosis (Chapter 4). The cut-offs were defined for post-menopausal women and have not been validated for pre-menopausal women or for men[223].

7.1.7 Osteoporosis in other conditions

7.1.7.1 Other GI conditions

In a systematic review, the rate of osteoporosis in coeliac disease ranged from 0-80% and for IBD ranged from 0-50% depending on the site of assessment[110]. Factors which contribute to bone loss in GI disease include malabsorption, systemic inflammation, secondary hypogonadism, and corticosteroid use. Other mechanisms include metabolic acidosis and possibly, the effects of proton-pump inhibitors[223]. In GI disorders, both a 'low-turnover' osteoporosis pattern (a normal degree of bone resorption with a reduced synthesis of bone matrix that is normally mineralised) and a 'high-turnover' osteoporosis pattern (enhanced activity of the osteoclasts causing accelerated bone resorption with an increase in bone formation, albeit insufficient to fully compensate for the degree of resorption resulting in net bone loss) are present[222].

7.1.7.2 Cystic fibrosis

Patients with cystic fibrosis develop PEI comparable to the exocrine deficiencies seen in chronic pancreatitis. Osteoporosis is common in patients with cystic fibrosis, and the reasons are multi-factorial. Malnutrition, malabsorption, low BMI, physical inactivity, chronic inflammation, low levels of insulin-like growth factor (IGF), delayed puberty / hypogonadism and the use of corticosteroids have all been implicated, resulting in the failure to achieve peak bone mass, as well as accelerated bone losses[227]. The pooled prevalence of metabolic

bone disease among adult cystic fibrosis patients has been reported to be as high as 23.5% (osteoporosis) and 38% (osteopenia)[228].

7.1.8 Reasons for low BMD in chronic pancreatitis

Low BMD may occur in patients with chronic pancreatitis for many of the same reasons as for the other GI diseases. Malabsorption and systemic inflammation may be exacerbated by poor dietary intake, low weight or weight loss, alcohol excess and smoking, all of which are likely to contribute to bone demineralisation and ultimately osteopathy.

7.1.9 Bone health guidelines for other conditions

There are several published consensus guidelines for bone protection in malabsorptive gastrointestinal conditions (including coeliac disease[111] and IBD[110]) which recommend the routine assessment of BMD and the routine supplementation of calcium and vitamin D. No bone health guidelines exist for chronic pancreatitis.

7.1.10 Prior studies examining bone density in chronic pancreatitis

The first study investigating osteoporosis in chronic pancreatitis was an uncontrolled study published from Argentina in 1997 that reported on just 14 patients[112]. In 2008, Dujsikova and colleagues[174] found that 5% of chronic pancreatitis patients had osteoporosis, while 39% in total had osteopathy including osteopenia, osteoporosis and osteomalacia. Haaber *et al*[94], showed that patients with advanced steatorrhoea had greater bone loss than those with preservation of exocrine function. Mann *et al*[109], published in 2003, found that those with chronic pancreatitis had a lower percentage of normal bone mineral density than controls. Regarding vitamin D, both Dujsikova and colleagues[174] and Mann *et al* reported an association between low BMD and serum 25-OH D levels, however Moran *et al*[112] did not, although with fourteen subjects it was underpowered to detect such an association. Prior to undertaking this study, there had been no studies examining the prevalence of osteoporosis in chronic pancreatitis in Ireland, the UK, or North America, and few studies from Europe. Similarly, there has been no systematic amalgamation of the available data on the

prevalence of osteoporosis in chronic pancreatitis. This chapter describes 1.) an investigation of the prevalence of osteopathy in Irish patients with chronic pancreatitis, and 2.) a systematic review and meta-analysis of the literature regarding the prevalence of osteopathy in chronic pancreatitis.

7.2 PART 1: An investigation of the prevalence of osteoporosis, osteopenia and vitamin D deficiency in Irish patients with chronic pancreatitis

7.2.1 Study rationale and objectives

Several studies have demonstrated a high prevalence of osteoporosis in chronic pancreatitis; however there have been few studies from Europe and none from Ireland or the UK. The lack of studies and consequent lack of guidelines on bone health means that osteoporosis is a neglected clinical problem for patients for chronic pancreatitis, potentially leading to significant morbidity in the future due to fractures. Given clinical observations within the Centre for Pancreatico-Biliary Diseases in Tallaght Hospital, we were concerned about the occurrence and risk of osteoporosis in chronic pancreatitis. We therefore developed a prospective study examining the nature and degree of the osteoporosis problem in chronic pancreatitis. In particular, clinical and social factors associated with accelerated bone loss were examined so that the causes of low BMD could be identified.

7.2.1.1 Study objectives

1. To determine the prevalence of osteoporosis and osteopenia in an Irish cohort of patients with chronic pancreatitis
2. To investigate serum 25-OH D and PTH levels in patients with chronic pancreatitis and matched controls, and to determine usage of vitamin D supplementation
3. To determine if factors including gender, age, smoking, disease severity and 25-OH D are associated with low BMD in patients and controls
4. To develop a statistical model to determine predictors of low BMD in patients with chronic pancreatitis.

7.2.2 Materials and methods

7.2.2.1 Study description

This study represented the second phase of a 2-part study on nutrition in chronic pancreatitis. The study description and recruitment process was described in Chapter 6 (with supplementary details provided in Chapter 4). Additional details of assessment are described below.

7.2.2.2 Assessment

7.2.2.2.1 Vitamin D supplement usage

Patients were asked about current vitamin D supplement usage, and these were subsequently grouped as 'any vitamin D supplement' which included vitamin D taken as part of a multi-vitamin, or 'vitamin D specific supplement' which included vitamin D taken as a high dose supplement (with or without calcium).

7.2.2.2.2 BMD assessment

All participants were invited to attend a DXA scan, which was performed in the Tallaght Hospital Radiology department using a Lunar Prodigy Advance densitometer, software version 11.40 (GE Healthcare, GE Medical Systems, Belgium, see Chapter 4)). DXAs were reported by a Consultant Radiologist who was blinded to the underlying clinical condition. Results were expressed as T-scores compared to values of young females. Diagnosis of osteoporosis or osteopenia was determined by the consultant Radiologist using the lowest T-score at any area. According to the WHO classification[128], between -1.0 and -2.5 SD were classed as osteopenia, while values below -2.5 were classed as osteoporosis. The following values were available: BMD, T-scores and Z-scores at the femoral neck (right and left) and total hip (left and right), and BMD, T-scores and Z-scores at the lumbar vertebrae (L1, L2, L3, L4 and L1-L4 average). For statistical analysis, the femoral neck was compared between patients and controls, due to the morbidity associated with fracture in this region (the right

femoral neck was chosen arbitrarily). Sample DXA assessment for severe osteoporosis and 'normal' BMD printouts are displayed in Figure 7.2 (A, B, C and D).

7.2.2.3 Statistics

Bivariate analyses were performed to evaluate group characteristics. Student's T-test was used to compare parametric data, and χ^2 for categorical data. Continuous data were divided into tertiles for comparison, where appropriate. One-way ANOVA was performed to compare group means and *post-hoc* (Tukey) analysis was completed, where appropriate. For multivariable analysis, backwards, stepwise linear regression was done to develop a model for the prediction of lowest T-score in patients. This involved starting with all possible predictive variables and testing them one by one for statistical significance and deleting those that were not significant from the model. For all analyses, *P* - values were two-sided, and a *P* - value of <0.05 was considered statistically significant. All statistical analyses were performed using Minitab, version 15.1 (State College, PA, USA). Advice regarding statistical analysis was provided by Tim Grant) C-Star, Dublin, Ireland).

7.2.2.4 Ethical approval

Ethical approval was given by the Joint Tallaght hospital / St James Hospital Ethics Committee (Appendix D).

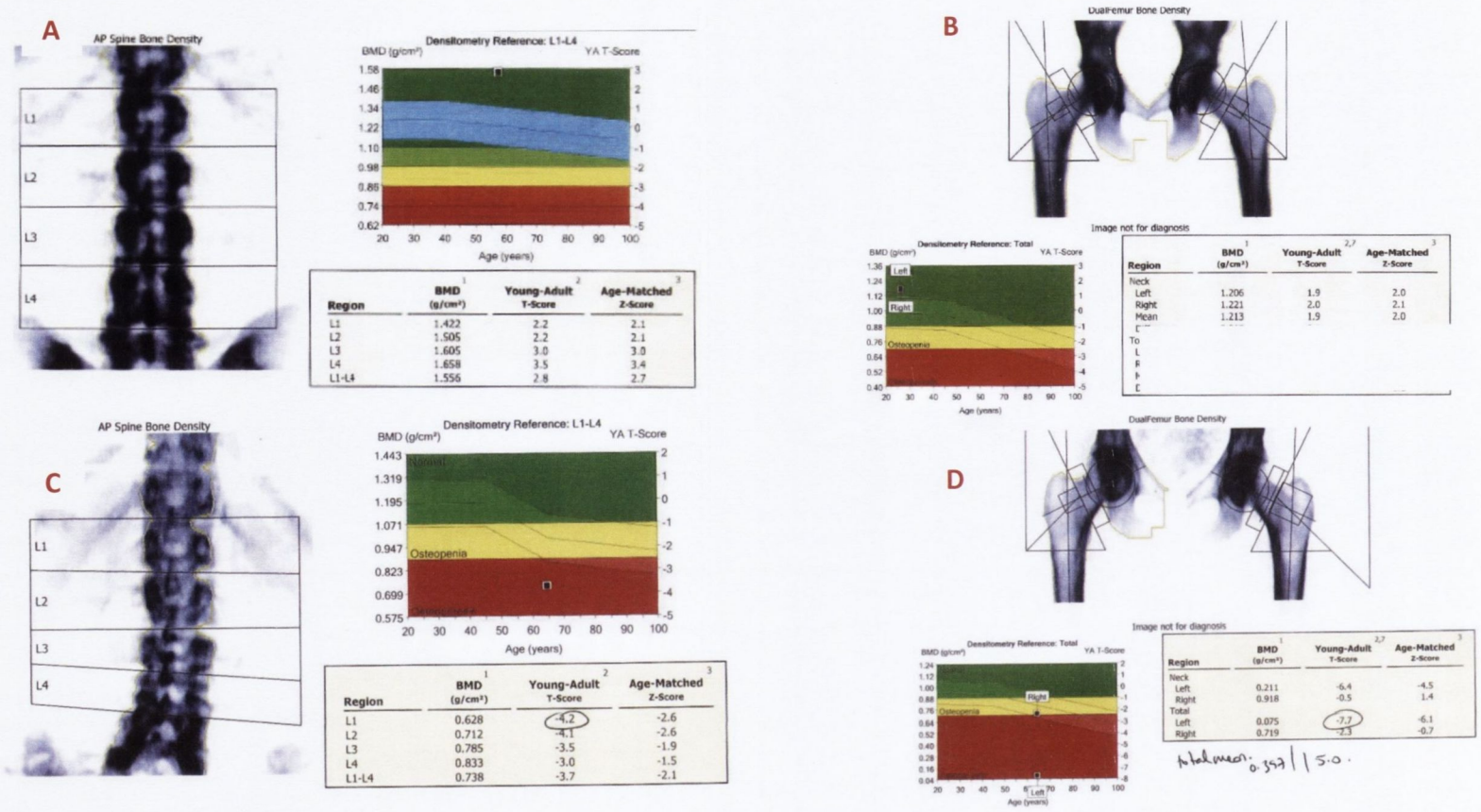


Figure 7.1 Sample DXA printouts from study group

A. BMD values for L1:L4 lumbar vertebrae in a 'normal' subject

B. BMD values for right, left and total femoral neck in a 'normal' subject

C. BMD values for L1:L4 lumbar vertebrae consistent with osteoporosis

D. BMD values for right, left and total femoral neck consistent with osteoporosis

7.2.3 Results

7.2.3.1 Group characteristics

Characteristics of the study groups were summarised in the previous Chapter (Table 6.1), showing that the groups were well-matched in terms of age, sex and education level.

7.2.3.2 Prevalence of osteoporosis and osteopenia

Fifty-three patients and 59 controls consented to a DXA scan. These groups were also well-matched and statistically similar. For these patients, mean (SD) patient age was 48.7 (11.8) and mean (SD) control age was 48.05 (10.7), (P = 0.889). Regarding sex, 75.5% of patients and 72.4% of controls were male (χ^2, P = 0.714). Regarding education level, 21% of patients finished 3rd level or higher compared to 24% of controls (χ^2, P = 0.655). In the patient group, 34% had osteoporosis (73.6% total osteopathy including 39.6% osteopenia). In contrast, 55.9% of controls had normal BMD and 44.1% had low BMD (10.2% osteoporosis, 33.9% osteopenia) (Figure 7.2). Table 7.2 details BMD T-scores at the right femoral neck, mean total hip and lumbar vertebrae (L1-L4) for patients and controls. The lowest T-score at any area is also provided for both subject groups. The T-score is compared between patients and controls for the right femoral neck and shows that T-score for patients is significantly lower than that of controls for this site.

7.2.3.3 Subgroup analysis

7.2.3.3.1 BMD and smoking

Among patients, there was a statistical association between smoking history and BMD. Those in the highest smoking tertile had significantly lower T-scores at the lumbar vertebrae (P 0.006, Figure 7.3) than those in the lower smoking tertiles. For the right femoral neck, there was a significant difference between the T-scores of the highest and lowest smokers (P = 0.007, Figure 7.4). For controls, the association between smoking and BMD was only significant at the right femoral neck. There was a significant difference in T-scores at the right

femoral neck across smoking tertiles (P = 0.007, Figure 7.5), but the difference in T-scores of the total hip (P = 0.07) and lumbar vertebrae (P = 0.08) fell outside of statistical significance.

7.2.3.3.2 BMD by disease severity, age and gender

There was no relationship between severity of chronic pancreatitis by the Cambridge severity classification and T-score at any site measured. Table 7.2 provides details for T-scores between subgroups (age and gender). For patients, when comparing across age tertiles using ANOVA, there was an overall effect with the lowest age tertile having significantly higher T-score than both the middle and upper tertile at the right femoral neck (P = 0.005, Figure 7.6), mean total hip (P = 0.037), but not at the lumbar vertebrae (L1:L4). Among controls, there was also an age effect seen at the right femoral neck (P = 0.008) but not at the total hip or lumbar vertebrae. The T-score at the right femoral neck was lower for male patients than male controls (P < 0.001), but this was not true for females. Among patients, there was no effect of gender for T-scores at any area. For controls, males had higher T-scores at the lumbar vertebrae and at the right femoral neck.

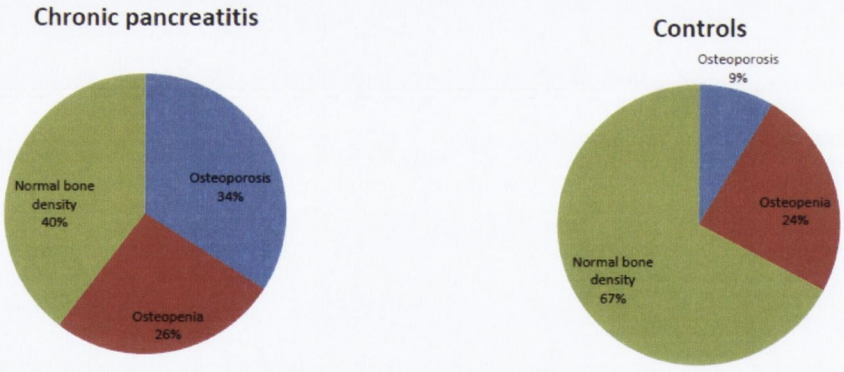


Figure 7.2 Rates of osteoporosis, osteopenia and normal BMD in patients with chronic pancreatitis compared to controls

Table 7.1 Osteoporosis prevalence for patients and controls

	Chronic pancreatitis (*n* = 53)	**Controls (*n* = 59)**	***P***
Osteoporosis	18 (34)	6 (10.2)	
Osteopenia	21 (39.6)	20 (33.9)	0.001§*
Normal bone density	14 (26.4)	33 (55.9)	

*Statistically significant, § Pearson's χ^2 test

Table 7.2 BMD values and T-scores for chronic pancreatitis patients and controls

	Chronic pancreatitis (n = 53 DXA scans)									Matched controls (n = 59 DXA scans)								
		Any area		Right femoral neck		Mean total hip		L1:L4 Lumbar Vertebrae			Any area		Right femoral neck		Mean total hip		L1:L4 Lumbar Vertebrae		p^{μ}
		Lowest T-score	SD	T-score	BMD	T-score	BMD	T-score	BMD		Lowest T-score	SD	T-score	BMD	T-score	BMD	T-score	BMD	
All patients	n	-1.77	1.47	**-0.754**	0.945	**-0.69**	0.979	**-0.815**	1.037	n	-0.885	0.14	**-0.104**	1.032	**0.071**	1.076	**0.034**	1.215	0.005*
Sex																			
Male	39	-1.76	1.08	**-0.925**	0.944	**-0.734**	0.995	**-0.783**	1.024	43	-0.736	0.98	**-0.002**	1.068	**0.255**	0.123	**0.310**	1.259	<0.000*
Female	14	-1.81	2.36	**-0.238**	0.948	**-0.562**	0.933	**-0.908**	1.075	16	-1.280	1.19	**-0.380**	0.934	**-0.433**	0.947	**-0.720**	1.098	0.79
$P^{\S}$				0.106		0.749		0.082					0.037*		0.1		0.017*		
Age[#]																			
1st tertile	12	-0.636	0.22	**0.278**	1.089	**0.173**	1.095	**0.109**	1.223	14	-0.325	0.63	**0.617**	1.126	**0.417**	1.120	**0.500**	1.271	0.55
2nd tertile	27	-2.081	1.17	**-1.026**	0.906	**-0.967**	0.946	**-1.201**	0.921	32	-0.981	1.21	**-0.109**	1.030	**0.087**	1.076	**-0.084**	1.202	0.002*
3rd tertile	14	-2.23	1.83	**-0.975**	0.914	**-0.500**	0.996	**-0.792**	1.113	13	-1.233	0.88	**-0.808**	0.944	**-0.317**	1.029	**-0.117**	1.195	
P†				0.003*		0.037*		0.071					0.008*		0.252		0.453		

*Statistically significant, μStudent's T-test comparing mean T-scores at the right femoral neck between patients and controls, §Student's T-test comparing mean T-score between genders at the right femoral neck, total hip and lumbar vertebrae for patients and controls

#Patients: first tertile <37.1 y; second tertile 37.1-57 y; third tertile >57 y; controls: first tertile <37.7 y; second tertile 37.8-56 y; third tertile >56 y

†ANOVA comparing mean T-scores between the age tertiles at the right femoral neck, total hip and lumbar vertebrae

Table 7.3 Backward stepwise linear regression showing factors predictive of lowest T-score in patients with chronic pancreatitis

	Coefficient	SE coefficient	T	*P*
Constant	0.546	0.87	0.63	0.533
Smoking tertiles [#]	-0.775	0.24	-3.25	0.002*
BMI categories [ϕ]	0.584	0.19	3.08	0.003*
Age, years	-0.046	0.014	-3.2	0.002*

*Statistically significant, #Smoking tertiles based on pack year history, ϕ BMI categories: underweight BMI ≤18.5 Kg/M2; normal weight BMI 18.6-24.9; overweight BMI 25-29.9; and obese or greater BMI ≥30

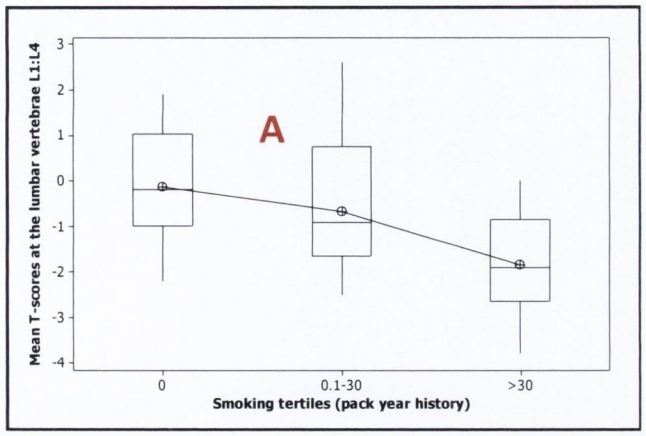
7.2.3.4 Predicting low BMD

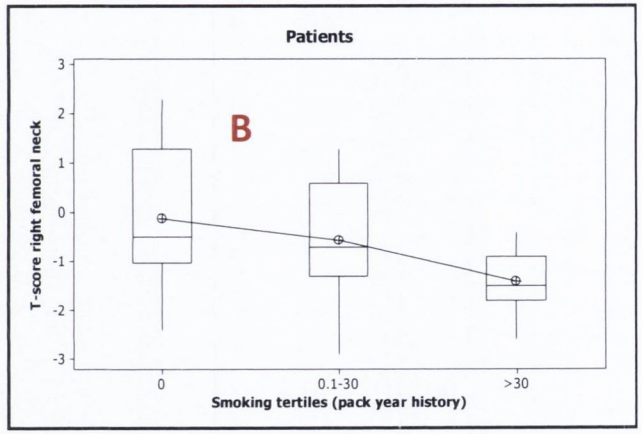
Using multivariable analysis, a model was developed for the prediction of lowest T-score in patients. In this model, heavy smoking history was predictive of a low T-score (P = 0.002), with each increase across the smoking tertiles there was a decrease in T-score of 0.775 on average. BMI was also predictive. A high BMI was predictive of a 'higher' lowest T-score (P = 0.003), with each increase across the categories of BMI having an increase in T-score of 0.584 on average. Age was also predictive, with every increase in age (years) having a decrease in T-score of 0.46 on average (Table 7.3). This multivariable analysis shows that smoking, BMI and age are all independently predictive of low BMD, while vitamin D, disease severity, faecal elastase-1 levels and education level were not significant in this model, and therefore not predictive.

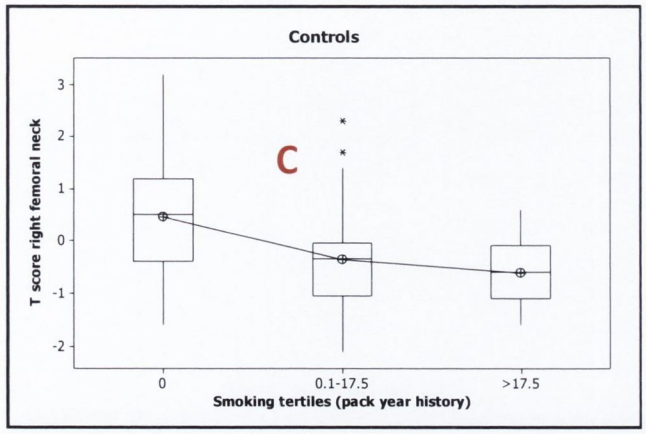
7.2.3.5 Vitamin D

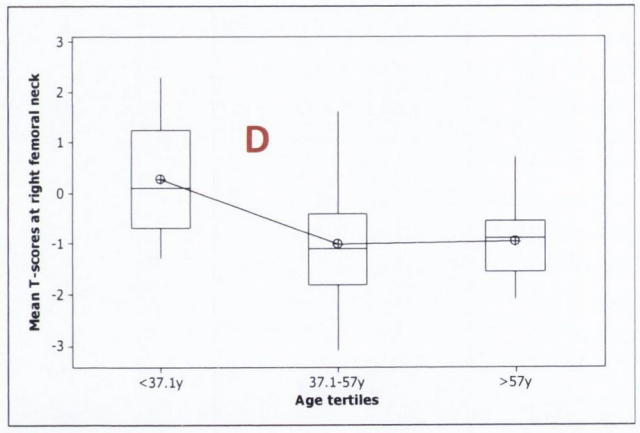
Vitamin D levels for patients and controls are detailed in Table 7.4. Mean (SD) 25-OH D levels were 47.5 (21.6) nmol/L in the patient group. There was no statistical difference in the 25-OH D levels of those who took a vitamin D-specific supplement or not (P = 0.324), or between those who took 'any' vitamin D-containing supplement (P = 0.118), nor was there a

difference between those who were assessed in winter/spring compared to summer/autumn (P = 0.23). Serum 25-OH D levels of patients were weakly and negatively correlated with PTH levels (P = 0.021, Figure 7.7). The mean 25-OH D levels of controls were 46.4 (21.6) nmol/L. There was no difference in 25-OH vitamin D levels between patients and controls (P = 0.798). For controls, there was no difference between those who were measured in winter/spring compared to summer/autumn (P = 0.82). Those who took 'any' vitamin D containing supplement had significantly higher vitamin D levels than those who did not (P = 0.01). There was no difference in the 25-OH D levels between those who took vitamin D-specific supplements and those who did not (P = 0.251). For controls, there was no significant correlation between vitamin D and PTH levels (P = 0.514, Figure 7.8).









A Figure 7.3 T-scores at the lumbar vertebrae (L1:L4) for patients divided by smoking tertiles (pack year history) (ANOVA, *P* = 0.006)

B Figure 7.4 T-scores at the right femoral neck for patients divided by smoking tertiles (pack year history) (ANOVA, *P* = 0.007)

C Figure 7.5 T-scores at the right femoral neck for controls divided by smoking tertiles (pack year history) (ANOVA, *P* = 0.007)

D Figure 7.6 T-scores at the right femoral neck for patients divided by age tertiles (ANOVA, *P* = 0.005)

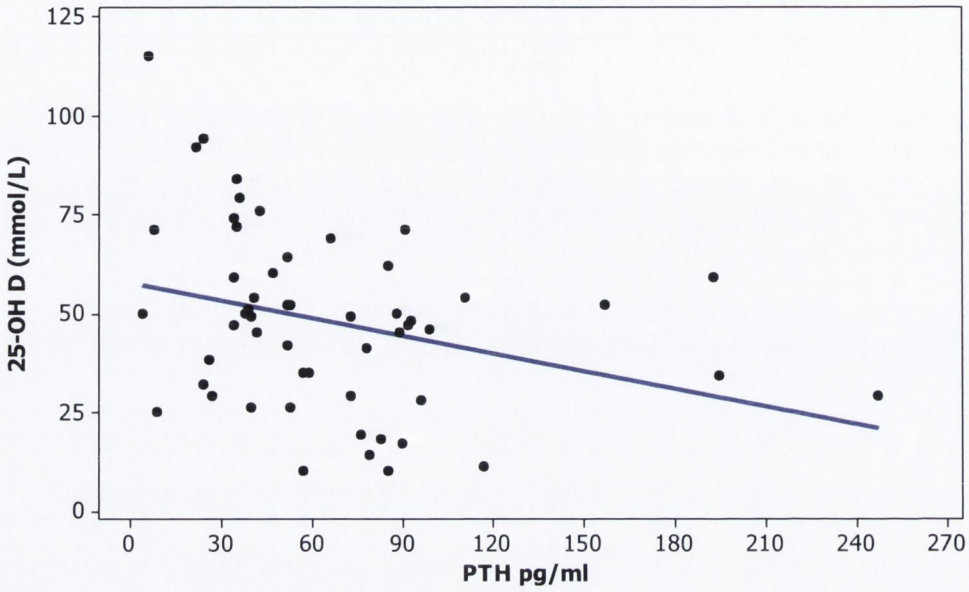


Figure 7.7 Scatter plot with regression line showing a low but statistically significant correlation (-0.314, P = 0.021) between serum 25-OH D levels and PTH among patients with chronic pancreatitis

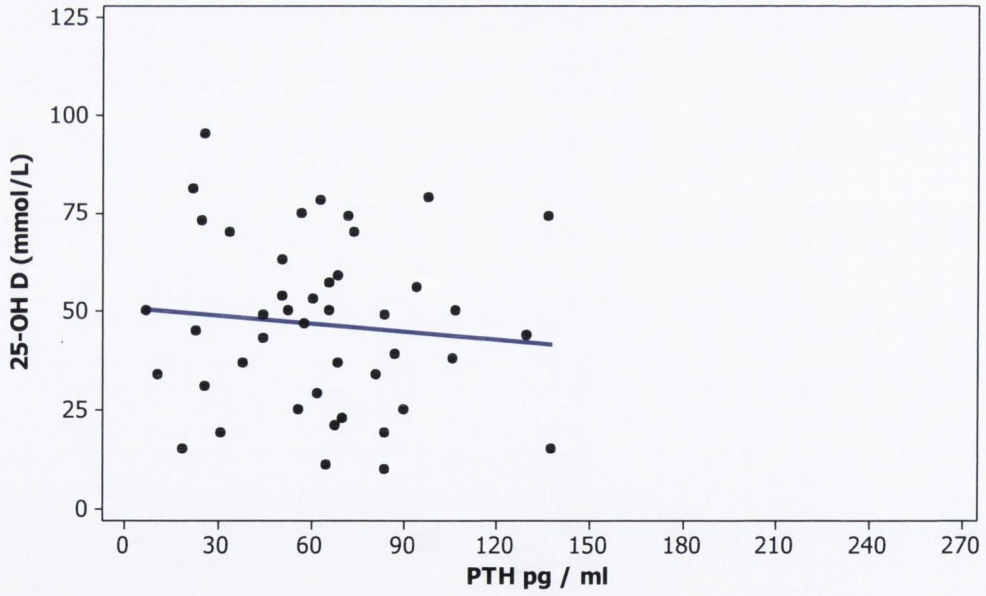


Figure 7.8 Scatter plot with regression line showing no correlation (-0.1, P = 0.514) between serum 25-OH D levels and PTH among controls

Table 7.4 Serum 25-OH D levels of patients and controls

		Patients			Controls		*P*
25-OH D mean (SD) nmol/L		47.5 (21.6)			46.4 (21.6)		0.798[μ]
Range		10-115			10-95		
Supplement use		**n**	**Mean (SD)**	***P***	**n**	**Mean (SD)**	***P***
'Any' vitamin D supplement[ϕ]	Yes	17	56.0 (27.4)	0.118	23	54.8 (23.1)	*0.01**
	No	45	44.3 (18.3)		25	38.7 (17.3)	
Vitamin D-specific supplement[#]	Yes	6	61.8 (36.6)	0.324	3	72.3 (29.5)	0.251
	No	55	45.3 (18.7)		45	44.7 (20.3)	
Winter/Spring[δ]		13	48.5 (24.5)	0.882	19	72.3 (29.5)	0.231
Summer/Autumn		48	47.4 (21.2)		24	44.7 (20.3)	

μStudent's T-test, ϕComparison of 25-OH D levels between those who were taking any vitamin D-containing supplement (including multivitamins or cod liver oil),*Statistically significant, #Comparison of 25-OH D levels between those who have taken a vitamin D-specific supplement (including vitamin D and calcium), δComparison of serum 25-OH D levels between those who had their levels assessed during during winter/spring and summer/autumn

7.2.4 Discussion

7.2.4.1 High osteoporosis prevalence in chronic pancreatitis

A third of patients with chronic pancreatitis had osteoporosis, which was more than triple the rate in the matched control group, and almost seven times what was reported in the most recent European study by Dujsikova *et al.*[174] The prevalence of both osteoporosis and osteopenia seen in this chronic pancreatitis group is striking, especially given that the patients are mostly male, and largely aged in their 40's. When analysing BMD for patients across age tertiles, there appeared to be no difference in T-scores for patients above age 37 years (the lowest tertile) – those in the middle and upper age tertiles had statistically similar T-scores. Compared to controls, T-scores for patients in the middle age tertile (37 years to 50 years) were significantly lower. Therefore it appears that in chronic pancreatitis, the protective effect of age only applies for the youngest patients. Those in middle age appear to have an accelerated risk of BMD loss. For patients with chronic pancreatitis, this age effect was significant at the total hip and right femoral neck – which represents significant morbidity and mortality in the event of a fracture. The risk of fracture increases by a factor of 1.4-2.6 for each SD decrease in BMD[110]. Therefore, the high osteopathy prevalence is likely to translate into future fractures as young patients with premature osteoporosis have the additional risk factor of increasing age to augment their fracture risk considerably in the future.

7.2.4.2 Subgroup associations

7.2.4.2.1 Smoking

Heavier smokers had the greatest loss of BMD for both patients and controls. However, for patients the effect was significant at the lumbar vertebrae and total hip, while in controls, the effect was significant only at the right femoral neck. In controls, smoking was associated with education level: those who finished third level education or higher were two and a half times more likely to be 'never' smokers than those who completed first or second level only. Therefore, for controls a lower smoking history might be accompanied by other features of high socio-economic status including diet, physical activity, finance and supplement usage –

all of which could influence bone health to some degree. In contrast, among patients, there was no difference in smoking according to education level. As those who smoked the most had the greatest loss of BMD, smoking may be a driver of bone mineral loss independent of socio-economic status. A growing body of evidence shows that cigarette smoking is a risk factor for osteoporosis, although the nature and magnitude of the relationship remains uncertain. In a meta-analysis of 86 studies[229], smokers had a significantly reduced bone mass compared with non-smokers (both ex- and never-smokers) at all bone sites, but particularly at the hip. The effects were greater in men, in the elderly and were dose-dependent. Whether or not smoking has a distinct toxic effect on bone micro-architecture, acts to displace bone-important nutrients, affects hormones or enzymes involved in bone regulation, or damages blood supply to the bone is open to debate. Importantly, smoking is a modifiable lifestyle factor, although it is not known if smoking cessation would prevent or reverse BMD loss in these patients. Notably, smoking is a risk factor for developing chronic pancreatitis[50, 230-231], although frequently under-recognised[232].

7.2.4.2.2 Disease severity

Contrary to what was found in other studies[94, 109], loss of BMD did not appear to be associated with disease severity, with the highest losses seen in the moderately severe group. This is surprising given that the most marked pain, nutritional deficits and exocrine dysfunction are seen when the disease is at its most severe. The fact that there was no identifiable linear relationship between chronic pancreatitis severity and BMD indicates that bone loss might be driven by factors additive to the disease process. This finding may also be indicative of problems with current severity stratification methods. The Cambridge classification used in this study provides a clinically utilisable system based on ERCP findings. However, it does not address the issues of exocrine and endocrine insufficiency or the presence of extra-pancreatic complications[54]. Therefore, along with other factors, this may account for the failure to find a relationship between BMD and disease severity.

7.2.4.2.3 Vitamin D

Average serum 25-OH D levels were in the 'insufficient' range for both patients and controls, although surprisingly not different between the two groups. One possible explanation for this may relate to higher vitamin D supplementation levels among patients (along with the fact that taking vitamin D supplements was not an exclusion criterion for recruitment). In addition, controls were heavier on average than patients. Thus, vitamin D might be sequestered in adipose tissue, leading to lower bio-availability[233]. For populations living at Northern latitudes such as Ireland, vitamin D deficiency and insufficiency is a public health problem due to the lack of vitamin D-producing rays for much of the year. The low levels are likely to contribute to the overall high osteopathy levels seen in both patients and controls. Supplementation may help to increase vitamin D levels – the present data showed that supplementation was associated with higher levels, at least in healthy subjects. For patients with chronic pancreatitis, routine vitamin D supplementation is probably necessary. Only 10% of dietary calcium is absorbed in a vitamin D deficient state, but in the vitamin D sufficient patient, calcium intake must also be adequate to prevent loss of BMD. Calcium absorption studies would help to determine what level of dietary calcium intake would be required in chronic pancreatitis. An intake of 1,000mg per day is recommended for patients with coeliac disease[110], so it is feasible that a similar level might be required in chronic pancreatitis.

7.2.4.3 Comparison to previous studies

In the first study to examine low BMD in chronic pancreatitis (published in 1997 by Moran and colleagues)[112], they reported that 13 of 14 subjects with steatorrhoea had osteopathy (3 of 14 patients had osteoporosis). Despite the obvious shortcomings of such a study, in particular the small sample size (which included men only) and lack of a control group, this study was the first to highlight the problem of bone demineralisation in chronic pancreatitis. Three years later, Haaber *et al* published results from a Danish chronic pancreatitis group[94], reporting a higher overall osteopathy rate (84.4%) than in the present study. However, the prevalence of osteoporosis itself was lower (22.4%). The Danish study was also limited by the lack of a control group, nor did they find any factors predictive of low BMD. In 2003, Mann

and colleagues reported on BMD in a German chronic pancreatitis population[109]. They provided results for the Ward's area of the hip (rather than providing T-scores or Z-scores) and found that those with chronic pancreatitis had values that were 92.2% of normal, compared to controls who had values that were 97.1% of normal. However, by reporting the Ward's area, the results are not comparable to the other studies available. Moreover, the AGA stated that the Ward's area has been largely abandoned as a measure of reduced BMD due to its poor reproducibility[222]. This study is therefore of limited usefulness as comparative data. Dujsikova *et al* reported a relatively low prevalence of osteoporosis in their study from the Czech Republic, published in 2008[174]. They found only 5% osteoporosis and 26% osteopenia (although they reported this as a high level). They also reported an 8% prevalence of osteomalacia, the method of diagnosis for which was unclear from the paper. It may be that those with vitamin D deficiency were classed as osteomalacia due to the relationship between vitamin D deficiency and this condition, but this was not specified in the text, nor was there a mention of bone biopsy. As discussed in Section 7.1.2, it is not possible to distinguish osteoporosis and osteomalacia on a DXA scan, nor do biochemical / clinical findings differentiate them. Therefore, this represents a significant limitation of the Czech study. Since completion and publication of the present study, several other studies have been published on the topic, including two from India[210, 234], and most recently, one from the Netherlands[191]. These are further discussed in Part 2 of this Chapter.

7.2.4.4 DXA as a method of assessing bone density

DXA is currently the gold standard for bone mass measurement. Advantages include the fact that it is quick (typically 10-30 minutes), can be used to scan areas of greatest clinical importance or relevance (e.g. spine of femoral neck), may be also used to measure body composition, and is safe (the radiation amount is of negligible risk at a fraction of the annual normal background radiation). However it also has several disadvantages:

- DXA has a measurement error of 5-6% (although this is classed a 'small' error thus enabling its use as a tool to diagnose osteoporosis and to assess fracture risk)

- BMD may be over-estimated in anteroposterior measurements of the lumbar spine due to degenerative changes
- Hip measurements are less susceptible to degenerative changes, however are affected by patient positioning and by hip rotation and therefore the use of standardised operator techniques is vital
- Previous fractures, surgery and Paget's disease can affect hip BMD results
- Reproducibility is influenced by instrument, operator and subject-dependant factors
- Due to differences in calibration, variability may exist between machines

7.2.4.5 Diet and chronic pancreatitis

This study is limited by the fact that dietary intake was not measured, nor was it measured in the other studies investigating this topic. It is probable that poor intakes of calcium are related to lower BMD. A few studies have examined dietary intake in chronic pancreatitis. Vaona and colleagues[97] reported dietary intake of 40 chronic pancreatitis patients who were in remission for more than 6 months compared to 75 matched controls. They reported on energy, carbohydrate, fat and fibre intake, as well as cholesterol and alcohol intake. However, they did not examine intakes of calcium or vitamin D. Turner *et al* examined incident cases of acute pancreatitis to determine the dietary patterns that characterise those with underlying chronic pancreatitis[235]. This study involved a detailed analysis of dietary intake including micronutrients folate, vitamin A and vitamin C. However, calcium and vitamin D intakes were not determined. In a study from Spain examining the role of the diet in the age of diagnosis of chronic pancreatitis and the probability of developing complications, a detailed analysis was performed on the intake of dietary fat, but the intakes of calcium and vitamin D were similarly not reported[236].

7.2.4.6 Bone histomorphometry

Assessment of bone by histomorphology was not an objective of the current study for several reasons. A bone biopsy procedure is invasive, expensive and complex - factors which limit its widespread clinical application[222]. However, although not indicated for most clinical

cases of osteoporosis, biopsy may be useful in providing important information about pathological processes[237]. Its most important clinical application is in the diagnosis of osteomalacia[222]. Other specific indications include diseases such as Paget's disease of the bone, primary bone tumours, or bone metastases[237]. Additionally, bone biopsy might be indicated in some cases for precisely defining the mechanisms of bone loss in osteoporosis, or may be used to evaluate the effect of various therapeutic manoeuvres on bone cell function[237]. Given its invasive nature, studies investigating bone histomorphometry are not plentiful in chronic pancreatitis. A South African study examined cortical and trabecular iliac crest bone in patients with alcohol-induced chronic pancreatitis by histomorphometry for microarchitectural and bone-turnover abnormalities[238]. The study was case-controlled: thirteen African males with alcohol-induced chronic pancreatitis were compared to 37 African males without chronic pancreatitis. Pre-biopsy tetracycline double-labelling of bone permitted measurement of time-based bone formation variables. They found that cortical thickness, endocortical thickness, trabecular thickness and bone volume were lower in patients than controls. Markers of bone turnover were also lower in patients than controls, as were serum vitamin D and magnesium levels. This study was limited by the use of cadaver bone samples among the controls (those who had died in road traffic accidents or by assault), as well as the small patients numbers. Nevertheless, this study represents the first and only study to date to investigate bone histomorphology in chronic pancreatitis.

7.2.4.7 Risk of fracture in chronic pancreatitis

As BMD decreases, the risk of fracture increases, and therefore low BMD in patients with chronic pancreatitis should (in theory) translate into fractures in the future. Ultimately, bone fracture is the most important endpoint of osteoporosis, as the disease itself is painless and symptom-free. However, there is a lack of published prospective data on the prevalence of fractures in chronic pancreatitis. In a retrospective cohort study, Tignor *et al* investigated the prevalence of bone fractures in chronic pancreatitis compared to other 'high-risk' GI conditions[239]. The study examined low-trauma fracture prevalence in one institution (Brigham and Women's Hospital, US) over a ten-year period from 1998 to 2008 (low trauma or 'fragility' fractures of the vertebrae, hip or wrist being the most likely to be related to

osteoporosis). The fracture prevalence for chronic pancreatitis was 4.82% compared to 5.0% for coeliac disease, 3.0% for Crohn's disease, 5.43% for gastrectomy and 4.83% for cirrhosis. The prevalence for controls was 1.13%. The odds of fracture was 2.4 for chronic pancreatitis, compared to 2.7 for coeliac disease, 1.7 for Crohn's disease, 2.5 for gastrectomy and 2.6 for cirrhosis. This study provided evidence for the first time that those with chronic pancreatitis have at least the same risk, or even a higher risk, of suffering an osteoporosis-related fracture than those with other GI diseases which are already considered 'high-risk'.

7.2.4.8 Bone metabolism in chronic pancreatitis

Biochemical markers that reflect the processes of bone resorption and bone formation can be measured in blood and urine. Utilisation of such markers in chronic pancreatitis may provide some insight into the mechanisms of bone loss in this condition. However, little is known about how altered bone metabolism may underpin chronic pancreatitis-related osteoporosis. Similarly, little is known about how chronic inflammation affects bone turnover in chronic pancreatitis. Chapter 8 describes a study investigating bone turnover in patients with chronic pancreatitis.

7.2.5 Study limitations and strengths

7.2.5.1 Limitations

- As discussed in the limitations of Chapter 5, this cohort study was conducted in a single institution, and as this is a tertiary referral centre, there was potential for selection bias. Of the eighty-four patients identified as being eligible, twenty-two declined to participate or repeatedly did not attend appointments and no data is known regarding BMD for those patents, which may or may not deviate from the study results.
- Sixty-two patients were included, but only 53 consented to a DXA scan. Of the sixty-six controls, fifty-nine had a DXA scan. The small sample size reduces the power of the study. However, the sample size of this study is typical of studies of patients with chronic pancreatitis. Of the previous studies on this topic, the sample sizes ranged

between 14 and 73 patients[94, 109, 112, 174]. In addition, despite the lower power, statistically significant differences were detected.

- This study did not record the following information, which would have been valuable and relevant to the topic: history of low-trauma fracture, dietary intake (in particular of vitamin D and calcium), measurement of sunlight exposure, markers of inflammation (outside of CRP), bone histomorphometry, or biochemical bone markers.
- The results were centred on T-scores rather than Z-scores (although the latter were available). Some previous studies provided Z-scores rather than T-scores.[94, 210] However, the present study included an age-matched control arm. Moreover, the AGA stated that the use of Z-scores may conceal normal age-related loss, thereby underestimating fracture risk[222].
- Self-reported intake of alcohol, smoking, and vitamin D supplementation introduces a potential source of reporting bias.
- The study group were heterogeneous in terms of aetiology, gender and age. Nevertheless, they were representative of the chronic pancreatitis population to hand.

7.2.5.2 Strengths

- This study had a control arm, while most of the previous studies on this topic did not[94, 112, 174]. The AGA stated that without the inclusion of appropriate healthy controls, it is possible to overestimate or underestimate the apparent prevalence of osteoporosis[222].
- The DXA scans were conducted on one single calibrated DXA scanner located in the Radiology department of a university-affiliated teaching hospital and was subject to stringent standardisation in terms of protocol.
- All anthropometric assessments were done by one investigator which reduces the potential for error due to inter-observer variability.
- Data from this study may serve as baseline data for future possible follow-up studies including the prevalence of fractures.

- Several studies to date have been published on this topic from other European countries, including Denmark[94] and the Czech Republic[240]. However, this was the first study to be published on patients with chronic pancreatitis from Ireland or the UK.

7.3 PART 2: A systematic review of the prevalence of osteoporosis and osteopenia in patients with chronic pancreatitis

7.3.1 Brief introduction and objectives

The variable results and heterogeneous nature of the published studies, coupled with the lack of guidelines on osteopathy in chronic pancreatitis, have lead to a degree of uncertainty regarding the management of bone health for this disease. To address this uncertainty and to make the data more broadly accessible, a systematic review of the literature, along with a meta-analysis of the data was undertaken. The objectives were to calculate a pooled prevalence of osteoporosis and osteopenia in patients with chronic pancreatitis as well as to undertake a systematic qualitative review of the literature.

7.3.2 Methods

7.3.2.1 Criteria for consideration of studies

The types of studies considered for inclusion were studies of prevalence including: case-controlled, cohort, and cross-sectional studies. Both controlled and uncontrolled trials were included. Participants were patients of either sex with a diagnosis of chronic pancreatitis. Participants were limited to adults only (>18 years), but studies that included both adults and children were not excluded in the first instance. The outcome measures of interest were bone density measured by DXA (T-scores or Z-scores), and where available, BMD (g/cm^2) and BMC (g/cm).

7.3.2.2 Search details

The following bibliographic databases were searched for studies on chronic pancreatitis and osteoporosis

- Ovid MEDLINE (1946 to end October 2012)
- Elsevier EMBASE (1980 to end October 2012)

- SciVerse SCOPUS (1966 to end October 2012)

No date or language restrictions were used, but searches were limited to humans. Searches were conducted during October 2012, and search updates were set up to automatically send updates to the authors from MEDLINE, EMBASE and SCOPUS. The last update considered for inclusion was sent at the end of October 2012. Two reviewers conducted separate searches, and both reviewers were unblinded (no restrictions to journal names or authors). The search strategy was developed for Ovid Medline and translated for use on EMBASE, and SCOPUS. A search for articles with combinations of subject headings and key words relating to "Pancreatitis, Chronic" or "exocrine Pancreatic Insufficiency" and "Bone Density" or "Absorptiometry, Photon" or "Bone Diseases, Metabolic" was conducted. Further searches were performed by scanning the reference lists of the primary and review articles to identify studies not found by the electronic search. Searches of conference proceedings were also conducted. Both independent reviewers were supported in developing search terms by medical librarians in separate institutions.

7.3.2.3 Study selection criteria

The full texts of potentially relevant papers were sought and the selection criteria applied (see Appendix K). Conference proceedings were considered if they contained adequate relevant information for review. Studies were selected according to pre-defined criteria. For both conference proceedings and full text papers, where there was missing data or a requirement for clarity, the study authors were contacted by e-mail. In the case of non English-language manuscripts, translations were done by Corporate Translation Services, Dublin, Ireland (ISO 9001:2008 Certified).

7.2.3.4 Assessment of quality of individual studies

The quality of the studies was evaluated independently by the two reviewers using Newcastle-Ottawa Scale (NOS) (Appendix L), which uses a "star" rating system to judge the quality of observational studies[241]. This scale awards a maximum of 9 stars to each study: up to 4 for selection of participants, 2 for comparability of participants on the basis of the design or analysis, and 3 for ascertainment of exposure. Scores of 0-3, 4-6, and 7-9 for low-, moderate-, and high-quality studies, were respectively assigned.

7.2.3.5 Data extraction and statistical analyses

Data extraction was done independently by the two reviewers using a predefined data extraction form. Osteoporosis rates and osteopenia rates were recorded (together termed 'overall osteopathy'). BMD and BMC were recorded where available for patients and controls. Additional data sought included: study design, gender, age, aetiology, DXA scanner used, sites assessed, exocrine function, disease severity and BMI. Details on statistical associations reported in the individual studies were recorded. Where osteopathy rates were available (number of events and number of patients), the data were deemed amenable to meta-analysis. Data were meta-analysed using Comprehensive Meta-Analysis software (version 2.2.064, USA) and forest plots were manually constructed using Excel (Microsoft Office 2007) as described by Neyeloff *et al*[242]. Data were presented as prevalence (%). A pooled estimation was computed using a random effects model to give a more conservative estimate of the prevalence allowing for variations between studies. Statistical heterogeneity between studies was calculated as I^2 (values range between 0% and 100% with values closer to 0 indicating less heterogeneity). The I^2 quantity describes the percentage of total variation across studies that is due to heterogeneity rather than chance. P values < 0.05 were considered statistically significant.

7.2.3.6 The MOOSE criteria

The MOOSE guidelines (Meta-analysis of Observational Studies in Epidemiology)[243] were adhered to where appropriate (see Appendix M).

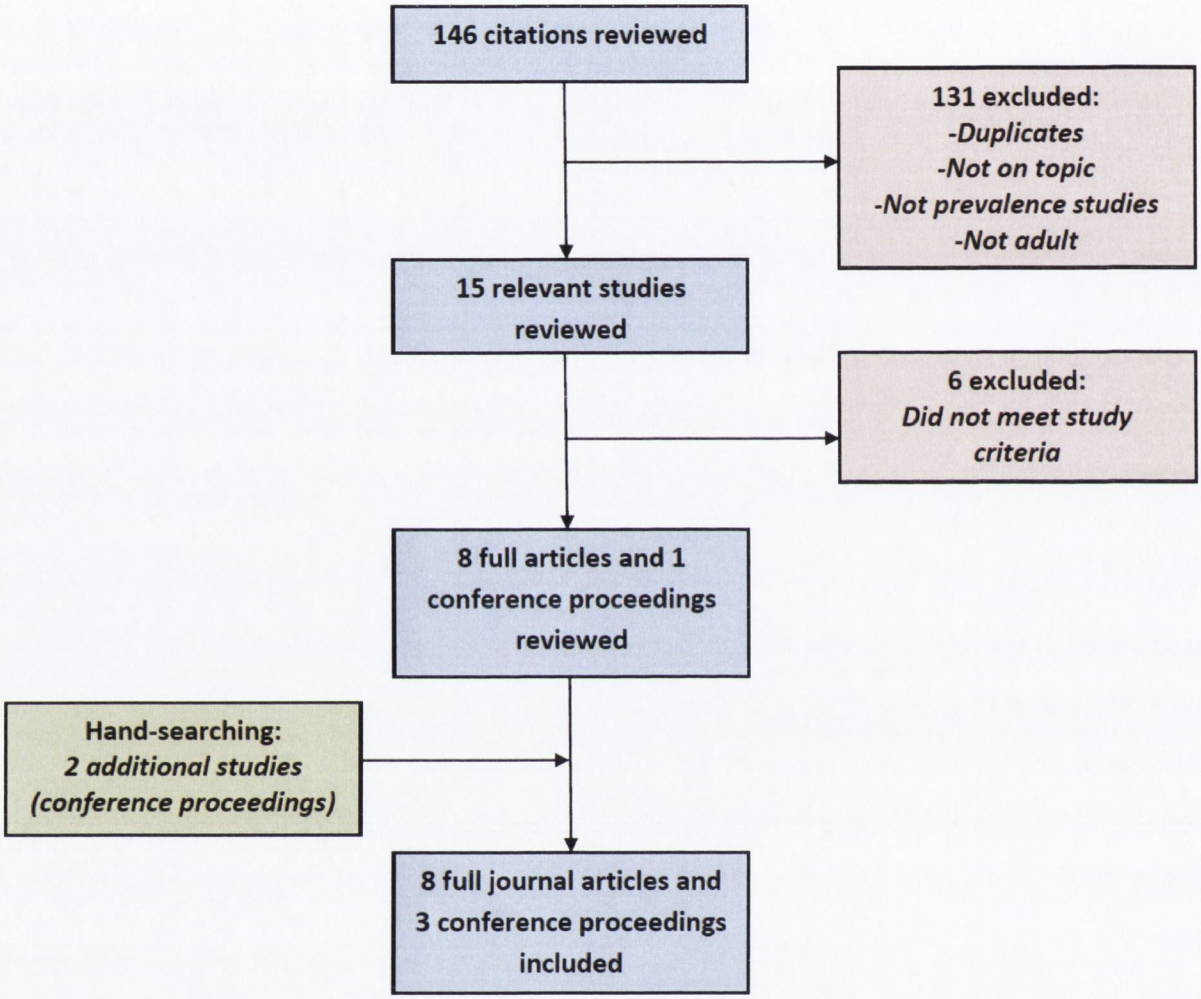


Figure 7.9 Flow diagram for the assessment of studies identified in the systematic review

7.3.3 Results

7.3.3.1 Search results

The search and selection process is summarised in Figure 7.9. Manual searches of the bibliographies of relevant articles and reviews did not provide any further articles. Hand-searching through conference proceedings yielded two additional studies.

7.3.3.1.1 Summary of studies included

Eleven studies met the inclusion criteria and were included in the review (Table 7.5).[94, 109, 112, 172, 174, 210, 234, 244-247] Of these, 8 were full articles and 3 were abstracts of conference proceedings. In total, 555 patients with chronic pancreatitis underwent BMD assessment. One study[109] did not report absolute osteopathy prevalence rates and the data were presented as a percentage of normal. Therefore, of 513 patients with comparable data, 129 had a diagnosis of osteoporosis. Osteopenia results were available from 482 patients, with 175 patients fulfilling the criteria for osteopenia. Four of the 11 studies had a control arm,[109, 172, 210, 234] amounting to a total of 214 controls. Of these, only 94 controls had comparable osteoporosis data giving a diagnosis in 9/94 cases. Of the 11 studies, 8 were conducted in Europe, 2 in India and one in South America. More than half (6/11) were published during 2011 and 2012. One study[244] was in Russian and was available in abstract form only. Following correspondence with the author, the full-text version was obtained and translated into English. Three studies reported on men only,[109, 112, 234] and the mean ages of patients included were largely in the 40's and 50's, with the notable exception of the studies from India, both of which had considerably younger patients (mean 31 years and 36 years).[210, 234] There was a mixed aetiology for all studies with the exception of one, which included subjects with tropical chronic pancreatitis only. There was a variation in types of DXA scanners used (Table 7.6). All studies reported BMD at the lumbar vertebrae, but there was variation over the reporting of the hip (total hip, left, right, Ward's triangle). Details of BMD or BMC were reported by 3 studies only.[112, 172, 234] In the majority of studies, osteoporosis and osteopenia were defined according to T-scores (T-score between -1.0 and -2.5 SD, osteopenia; T-scores below 2.5 SD, osteoporosis). Two studies[94, 210] defined osteoporosis and

osteopenia according to Z-scores (Z-scores <-1 osteopenia, Z-scores <-2 osteoporosis). Most studies reported details of either exocrine function, disease severity, or both. Subgroup analyses were reported in all studies, and are summarised in Table 7.7 according to the presence of a statistical association, or 'no association'.

Table 7.5 Description of 11 studies included in the systematic review

	Author, year Country	Publication type/ Study design	Subjects (n)		Sex M/F	Age (yrs) (SD)	Aetiology	Meta-analysis
			Patients	*Controls*				
1	**Duggan (current study), Ireland**	**JA, Case-control**	**53**	**59**	**45/17**	**47.9 (12.5)**	**38.7% alcohol**	**Yes**
2	Sudeep et al, 2011 India	JA, Case-control	31	35	31/0	35.8 (9)	65% TCP 35% idiopathic	Yes
3	Joshi et al, 2011 India	JA, Case-control	56	100	38/34	31 (10)	100% TCP	Yes
4	Drozdov et al, 2010 Russia	JA, Cross-sectional	100	-	47/53	51 (10.2)	52% alcohol 48% biliary	Yes
5	Dujshikova et al, 2008 Czech Republic	JA, Cross-sectional	73	-	56/17	46.6 (13.2)	89% idiopathic 11% alcohol	Yes
6	Mann et al, 2003 Germany	JA, Case control	42	20	42/0	52.6 (13.5)	*Not specified*	No
7	Haaber et al, 2000 Denmark	JA, Cross-sectional	58	-	32/26	55 (11)*	79.3% alcohol	Yes
8	Moran et al, 1997 Argentina	JA, Cross-sectional	14	-	14/0	56	71% alcohol 29% idiopathic	Yes
9	Sikkens et al, 2012 The Netherlands	CPr, Cross-sectional	40	-	23/17	52(11)	50% alcohol 30% idiopathic 20% other	Yes
10	Skipworth et al, 2012 United Kingdom	CPr, Retrospective review	64	-	44/20	60	52% alcohol 25% idiopathic 11% biliary 12% other	Yes
11	Gubergrits et al, 2011 Ukraine	Cpr, Cross-sectional	24	-	*Not specified*	*Not specified*	*Not specified*	Yes

*Values only available for PEI group; JA journal article, CPr conference proceedings

Table 7.6 Prevalence of osteoporosis and osteopenia among chronic pancreatitis patients and controls

Study	DXA details	Sites	Chronic pancreatitis patients				Controls			
			Osteoporosis, n (%)	Osteopenia, n (%)	BMD (SD)	BMC (SD)	Osteoporosis, n (%)	Osteopenia, n (%)	BMD (SD)	BMC (SD)
Duggan (current study)	**Lunar Prodigy Advance**	**Total hip Right FN LV L1:L4**	**18 (34)**	**21 (39.6)**	**0.945**	**-**	**6 (10.2)**	**20 (33.9)**	**1.032**	**-**
Sudeep et al, 2011	QDR 4500	LV	9 (29)	-	0.891 (0.135)	51.9 (10.3)	3 (8.6)	-	0.946 (0.098)	50.51 (7.62)
[α]Joshi et al, 2011	QDR 4500	Left hip Distal radius LV	22 (39)	14 (25)	-	-	δ	δ	-	-
Drozdov et al, 2010	Lunar DPX 21200	Hip LV	39 (39)	18 (18)	-	-	-	-	-	-
[β]Dujshikova et al, 2008	Lunar	Whole proximal femur LV L1:L4	4 (5)	19 (26)	-	-	-	-	-	-
[#]Mann et al, 2003	Lunar Radiation	Ward's triangle LV L2:L4	DEXA WARD 92.2 (5.2)% normal	-	-	-	DEXA WARD 97.1 (3.1)% normal	-	-	-
[α]Haaber et al, 2000	Norland XR 36	Total body LV L2:L4	13 (22.4)	36 (62)	-	-	-	-	-	-
Moran et al, 1997	Lunar DPX	FN [μ]LV L2:L4	3 (21.4)	10 (71.4)	1.07 (0.05)	-	-	-	-	-
Sikkens et al, 2012	Lunar prodigy	Left femur LV L2:L4	4 (10)	18 (45)	-	-	-	-	-	-
Skipworth et al, 2012	*Not specified*	FN LV L1:L4	12 (19)	27 (42)						
Gubergrits et al, 2011	Explorer QDR	*Not specified*	5 (20.8)	12 (50)	-	-	-	-	-	-

αPresented as Z-scores; δ control values not discernible from text; βFurther 6 patients (8%) classed as 'osteomalacia'; #BMD values presented as % normal; μPresented for lumbar spine; FN femoral neck, LV lumbar vertebrae

7.3.3.1.2 Author contact

Further information or clarification of data was sought for 8 of the 11 studies. Replies were received from 5 of these.[172, 210, 244-246] In one case,[245] the authors provided data for 40 patients where the original conference abstract provided data for 28 patients only.

7.3.3.1.3 Study quality

On the basis of the NOS, four studies[109, 172, 210, 234], all of which were controlled, received greater or equal than 7 stars (of a possible 9 stars) and were classified as "high-quality" studies. The other studies, all of which were uncontrolled, received 3 stars or less and were classified as "lower quality". The conference proceedings were not amenable to quality assessment. There was 100% agreement between the two independent reviewers regarding the categorisation of studies into quality groupings.

7.3.4 Factors affecting BMD in chronic pancreatitis

7.3.4.1. Age at assessment

Counter intuitively, the four papers with the highest prevalence of osteoporosis (> 29%) had generally younger patients (mean age 31, 36, 48, 51 years) than those with lower osteoporosis prevalence (mean age 52, 53, 55, 56, 60 years), with one exception in the lower incidence group[174] (mean age 46.6 years). The two studies from India[210, 234] in particular had patients in the early to mid-thirties on average. There was, however, no observed age pattern when looking at the prevalence of overall osteopathy.

7.3.4.2. Gender

Three studies examined men only, while the rest included both genders. Only 3 studies reported testing for a gender effect, of which 2 found no difference regarding BMD[172, 210], only 1 study reported lower BMD in females *versus* males[244].

7.3.4.3. BMI

Patients from the 2 studies from India[210, 234] were notably lower in BMI than in other studies (predominantly tropical chronic pancreatitis aetiology), and had a high prevalence of osteoporosis. Both noted positive statistical associations between BMI and bone mineral density. All other studies had mean BMI in the 'normal range', with the exception of the Irish study[172] with a mean BMI marginally in the overweight range. The Irish[172] and UK[246] studies reported a statistical association with BMI (decreased BMI associated with decreased BMD).

7.3.4.4. Aetiology

All but one study[210] had a mixed aetiology (only tropical chronic pancreatitis patients). Owing to the mixed nature of the study groups, there were no apparent associations with BMD.

7.3.4.5. Exocrine function

Most studies reported PEI of varying degrees (one study[174] did not report on exocrine dysfunction). To assess pancreatic exocrine function six studies measured faecal elastase-1,[109, 172, 210, 244-247] three studies measured stool faecal fat[94, 112, 234] and the remaining study did not provide details on measurement method[246]. Two studies[112, 246] reported that *all* subjects had measurable exocrine impairment or clinical steatorrhoea. Five studies[94, 234, 245, 247] reported statistical associations between lower faecal elastase-1 levels (or high faecal fat) and reduced BMD, although one study reported the association only with BMC.[234] Three studies found no association. However of those, two[94, 172] reported PEI in less than half the group leading to smaller subgroup numbers, while the third[112] had a very low sample size (n = 14) and therefore was likely to be underpowered to detect subgroup differences if they existed.

7.3.4.6.Disease severity

Only 4 studies[109, 172, 174, 244] gave details of disease severity, and of these, only 2 provided classification according to the recognised Cambridge criteria.[109, 172] While one study found an

association with disease severity[109] (lower BMD in higher severity grades), the other did not.[172]

7.3.4.7 Vitamin D

Seven studies considered associations between low serum 25-OD D and low BMD, four of which found no association[94, 112, 172, 210]. Of the controlled studies (n = 4) two studies[172, 210] found that controls also had low serum 25-OD D, with no statistical difference between controls and patients. Conversely, two groups[109, 234] reported differences between control and patient serum 25-OH D.

7.3.4.8. Smoking

Three studies,[172, 245-246] all of which were published in 2012, considered the relationship between smoking and bone demineralisation. While two of these found no association, one[172] reported a statistically significant relationship between heavy smoking and reduced BMD.

7.3.4.9 Duration of disease and symptoms

One Indian study[234] found a statistical association between duration of *symptoms* and low BMD, while one study[244] reported a link between duration of *disease* and low BMD. Two other studies which considered the relationship between disease duration and BMD found no such relationship.[94, 246]

Table 7.7 Details of disease severity and statistically significant associations between BMD and specific factors

Study	Exocrine function	Disease severity	BMI mean (SD) (chronic pancreatitis)	Subgroup analysis – association with low BMD	
				Statistical association	*No association*
Duggan et al (current study),	**30.4% PEI**	**Cambridge classification 27.4% severe**	**25.6 (5)**	**Increasing age, heavy smoking history, lower BMI**	**Disease severity, faecal elastase-1, vitamin D, sex, education level**
Sudeep et al, 2011	69% steatorrhoea	*Not specified*	18.46 (2.86)	Duration of symptoms, Lower BMI	Vitamin D
Joshi et al, 2011	46% steatorrhoea	*Not specified*	19 (3.1)	Lower BMI	Vitamin D
Drozdov et al, 2010	59% PEI	44% 'complicated disease'	7% underweight 61% normal weight 26% overweight 6% obese*	Lower faecal elastase-1, duration of the disease	-
Dujshikova et al, 2008	*Not specified*	27.4% severe	*Not specified*	Lower Vitamin D	-
Mann et al, 2003	Mean Faecal Elastase-1 92.2 (5.2)	Cambridge classification 20% severe	*Not specified*	Disease severity, lower faecal elastase-1, vitamin D	PTH, OC, CICP, BAP
Haaber et al, 2000	44.8% PEI, steatorrhoea	*Not specified*	22 (3)[α]	-	Disease duration, vitamin D, PTH, calcium, PEI, steatorrhoea
Moran et al, 1997	All subjects steatorrhoea	*Not specified*	22.6 (3.2)	-	Alcohol, faecal fat, secretin test, BMI, age, vitamin D, PTH, serum calcium
Sikkens et al, 2012	70% PEI	*Not specified*	24 (5)	Lower faecal elastase-1	Smoking, alcohol
Skipworth et al, 2012	All subjects PEI	*Not specified*	23.3	Lower BMI, DM	Aetiology, smoking, bone biochemistry, disease duration
Gubergrits et al, 2011	*Not specified*	*Not specified*	*Not specified*	Lower faecal elastase-1	-

*Classed as BMI >28 Kg/M^2; [α]Values only available for PEI group; BAP bone-specific alkaline phosphatase, CICP carboxy-terminal propeptide of type I pro-collagen

7.3.5 Meta-analysis of osteoporosis prevalence

7.3.5.1 All studies

Of the 11 studies that met the criteria for systematic review, 10 were deemed eligible for meta-analysis. One study[109] differed considerably in terms of data presentation and was not included. Attempts to contact the study authors for further information were not successful. Figure 7.10 illustrates the prevalence of osteoporosis in 10 chronic pancreatitis studies. Assessment of statistical heterogeneity gave an I^2 value of 73.6%, indicating considerable heterogeneity. Although statistical and clinical heterogeneity between studies means that any pooling of prevalence data must be interpreted with some caution, a random effects model gave an overall prevalence rate of 23.4%. Osteoporosis prevalence ranged from 5.0 to 39.3%. Figure 7.11 summarises the prevalence of overall osteopathy (osteoporosis and osteopenia), and adopting the same interpretive constraints, with a random effects model the pooled osteopathy prevalence was calculated at 65%, with an osteopathy ranging from 39.7 to 92.8%. In one study[174] the authors reported osteomalacia in 6 subjects, and although it was unclear how this was diagnosed (attempts to contact the authors were unsuccessful), when calculating the overall osteopathy event rate, osteoporosis, osteopenia and osteomalacia were included.

7.3.5.2 Excluding studies with tropical pancreatitis aetiology

The meta-analysis was redone excluding the studies from India which included mostly tropical chronic pancreatitis patients associated with severe malnutrition. When the two studies from India[210, 234] were removed the pooled prevalence for osteoporosis was slightly lower at 20.6% (Figure 7.12), while upon removal of the remaining Indian study[5] from the overall osteopathy analysis, the pooled prevalence for overall osteopathy was very similar (65.4%) to the original value (Figure 7.13). Regarding controls, of two studies with usable osteopathy data, the osteoporosis rate for controls ranged from 8.6–10.2%, while the osteopenia rate for controls from one study was 33.9%.

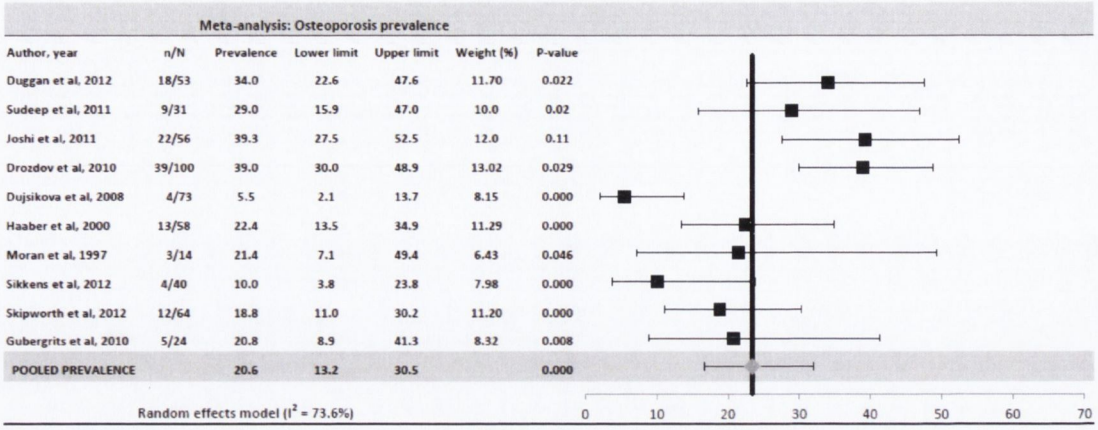


Figure 7.10 Forest plot of the pooled prevalence of osteoporosis in chronic pancreatitis using a random effects model

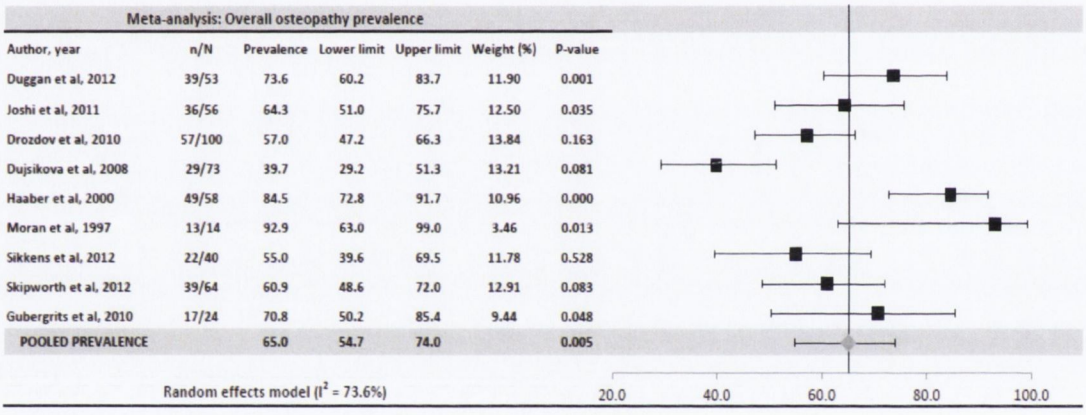


Figure 7.11 Forest plot of the pooled prevalence of overall osteopathy (osteoporosis and osteopenia) in chronic pancreatitis using a random effects model

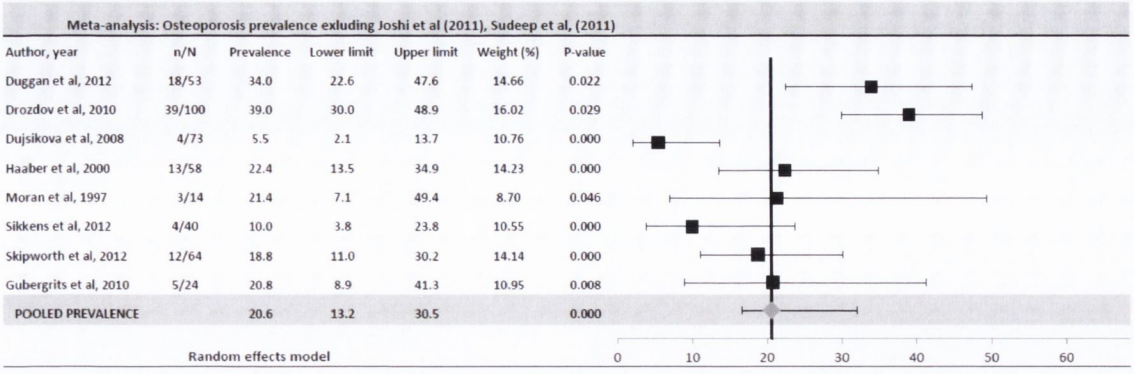


Figure 7.12 Forest plot of the pooled prevalence of osteoporosis in chronic pancreatitis using a random effects mode, excluding studies with tropical pancreatitis as a predominant aetiology

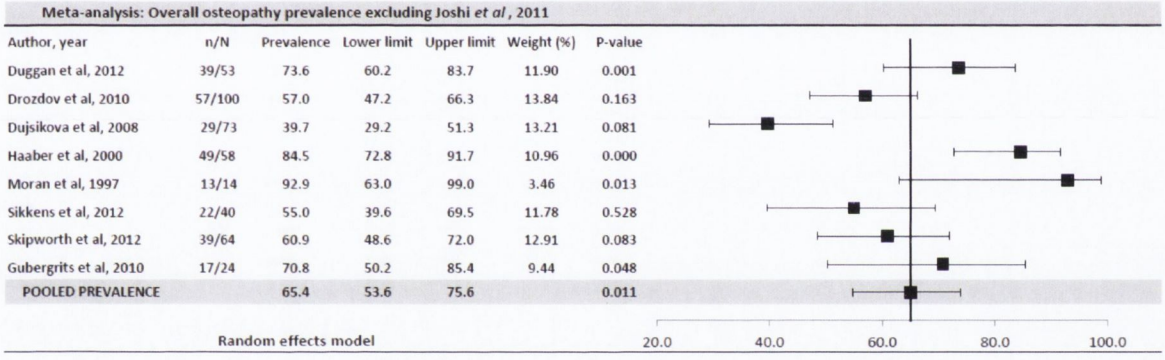


Figure 7.13 Forest plot of the pooled prevalence of overall osteopathy (osteoporosis and osteopenia) in chronic pancreatitis using a random effects model, excluding studies with tropical pancreatitis as a predominant aetiology

7.3.6 Discussion

In the first systematic review on the prevalence of osteoporosis and osteopenia in chronic pancreatitis, eleven studies were reviewed. A high prevalence of osteoporosis in chronic pancreatitis, along with a high prevalence of overall osteopathy was demonstrated. According to the available data, the prevalence of osteoporosis in chronic pancreatitis may be as high as 1 patient in 4. Similarly, by calculating a pooled prevalence as many as two thirds of chronic pancreatitis patients may have osteopathy (either osteopenia or osteoporosis). Due to the heterogeneous data and the small sample size in individual studies, making definitive or broad statements on subgroup associations is not warranted. Nevertheless, certain patterns were evident from the studies included. PEI was associated with lower BMD in 5 of 9 studies where it was measured. It is reasonable to assume that a reduction in enzyme production affecting nutrient absorption would affect BMD. As PERT is the mainstay of treatment for PEI[180] this finding supports the necessity of timely and adequate prescription of PERT, although there are no published data on the effect of PERT on bone density. Low serum vitamin D levels are probably contributory to low bone density in chronic pancreatitis due to malabsorption and diminished sunshine exposure in chronic illness. However, failure of the available data to show direct associations between serum vitamin D and low BMD may be due to seasonal variation in vitamin D levels. These data suggest that vitamin D deficiency may not be the main driver of bone demineralisation. Two of the high-quality studies included found that vitamin D levels in the affected populations, while low, were not different from controls. In certain aetiologies, malnutrition (as evidenced by low BMI) was a strongly associated factor. BMI is a recognised indicator of nutritional status and therefore this association may show that under-nutrition in chronic pancreatitis is an important contributor to loss of BMD. As female sex (post-menopausal) is a known risk factors for low BMD, a failure to identify a relationship between sex and low BMD is surprising and may suggest that factors relating to the chronic pancreatitis disease process itself are the drivers of bone demineralisation. Similarly, although one would expect older patients to have lower BMD due to the normal age-related bone demineralisation, there was no apparent association between age and BMD. Therefore, while it could be argued that the complications of chronic pancreatitis might cause death before the economic burden of

osteoporosis is realised, the studies in this review showed that osteoporosis is prevalent in a relatively young patient group. It is probable that increasing age and for females, menopause, will have an additive effect on osteopathy.

It is likely that the pathogenesis of low BMD is multifactorial and is driven by a mix of co-existing factors. Potential drivers of bone loss in chronic pancreatitis include limited mobility, malabsorption of calcium and vitamin D, chronic inflammation, and poor dietary intake and/or displacement of diet by smoking or alcohol. In coeliac disease and IBD, normal regulatory control of bone metabolism may be adversely affected by proinflammatory cytokines released from inflamed intestines as well as from mature T-cells.[248] The effect of chronic inflammation on bone metabolism in chronic pancreatitis has not been characterised.

As previously discussed, the BSG published guidelines for osteoporosis in IBD and coeliac disease in 2007.[110] In its systematic review, it reported 18 cross-sectional studies of BMD in Crohn's disease reporting an osteoporosis prevalence of between 0% and 50%. Whilst acknowledging the limitations of a pooled analysis, it reported that T-scores were within the osteoporotic or osteopenic range in over half of patients. In our study, the comparable figure was 65%, a finding which is even more striking when you consider that patients with chronic pancreatitis do not have the added risk factor of cumulative corticosteroid doses which are associated with reduced BMD in Crohn's disease.[110]

7.3.7 Study limitations and strengths

7.3.7.1 Limitations

- The clinical and methodological diversity of the included studies means that any conclusions, particularly of meta-analyses, must be interpreted with caution.
- While an overall meta-analysis of the prevalence was conducted, the data did not support a meta-analysis of the various subgroups.
- There is a possibility of case-selection bias in individual studies which may inflate the true prevalence. Similarly, publication bias may preclude the publication of 'negative'

studies which may further over-estimate the true prevalence. Studies differed in terms of patient type, disease severity and assessment methods.

- Individual studies had small sample size (n = <100; indeed one had only 14 patients) leading to wide confidence intervals.
- The reporting quality of included studies varied somewhat, with only four achieving high-quality scores, and four being classed as low-quality.
- The study published from Section 1 of this chapter was included in the systematic review in Section 2, and therefore the author was also a reviewer in the systematic review which has the potential to introduce bias in study assessment. However, the inclusion of two independent, blinded reviewers reduced this bias.
- Notably, only four of eleven studies included the recruitment of a comparative control arm.
- The amalgamation of studies from vastly different countries is a further limitation. For example, while eight of the studies originated in Europe, two were from India and one from South America. However, in the case of the studies from India, while the patients were younger than those in the European studies, the rates of osteoporosis and overall osteopathy were not vastly different and these studies were not considered outliers. Perhaps more importantly, most or all of the patients in the two studies from India had tropical chronic pancreatitis, which is associated with malnutrition. Therefore, bone demineralisation for this group may be partly secondary to undernutrition. However, when these studies were excluded from meta-analysis, the results were not greatly altered.

7.3.7.2 Strengths

- Despite the limitations, the systematic review was performed within the constraints of rigorous methodology.
- Two reviewers conducted study selection, data extraction and quality assessment independently. Each reviewer was supported by a medical librarian from different institutions to minimise potential bias. The data analysis was further supported by medical statisticians.

- Non-English language studies and conference proceedings were included, and therefore the studies yielded were a reflection of all the international research in this field, allowing the amalgamation of data for 555 chronic pancreatitis patients. All studies included in the review were from different centres and were by different authors.
- Intensive efforts were made to contact study authors to obtain additional information for clarity and completeness.

7.4 General conclusions

Data from the Irish cohort of patients demonstrated a notably high prevalence of osteoporosis and overall osteopathy. This data was further strengthened by the systematic review and meta-analysis which found that the pooled prevalence of osteoporosis from eleven studies was almost 1 in 4. Together, these merit the development of bone health guidelines for this patient group. These findings have direct implications for clinical practice. Bone-health assessment should form an integral part of the medical / nutritional workup of patients with chronic pancreatitis in order to prevent and treat osteoporosis and ultimately prevent fracture and its associated morbidity.

Chapter 8 An investigation into bone metabolism and systemic inflammation in chronic pancreatitis

As previously discussed in Chapter 7, loss of BMD in chronic pancreatitis is a multifactorial process, with factors such as disease severity, smoking, vitamin D deficiency, poor diet, and poor exercise all playing a part. The contribution of systemic inflammation to bone demineralisation in this disease has not been previously explored. This chapter describes an investigation into the relationship between inflammation and bone turnover in patients with chronic pancreatitis compared to matched controls. This chapter will also describe the anatomy and physiology of bone in greater detail.

8.1 Introduction

8.1.1 Osteoporosis

Osteoporosis is a systematic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.[249] In osteoporosis there is a normal mineral:collagen ratio, unlike that of other metabolic bone diseases such as osteomalacia (in which there is a failure to mineralise the newly-formed osteoid . While osteoporosis itself is a symptomless disease, the undesirable sequelae are low-trauma (fragility) fractures which are accompanied by considerable morbidity and mortality. For example, the mortality associated with a hip fracture is 15-30%, with most deaths occurring within the first 6 months.[250] Furthermore, despite the asymptomatic nature of the condition the presence of osteoporosis negatively affects QOL. A systematic review found that health-related QOL was poorer in patients with osteoporosis, even in the absence of vertebral fractures. [251]

8.1.2 Bone

Bone has three main functions; 1) it is the primary reservoir for calcium in the body, continuously exchanging calcium with the extracellular environment, 2) the haematopoietic

marrow located in cancellous bone supplies the body's cells, tissues and organs with erythrocytes, leukocytes and platelets, and 3) it has a mechanical role in supporting the body's tissues, protecting the internal viscera and providing sites of attachment for the muscles that effect body movement and locomotion.[252] There are two types of bone: woven (immature) and lamellar (mature). In woven bone, collagen fibres are arranged haphazardly and cells have no specific orientation. It acts as a temporary scaffold before being replaced by mature bone. It is found in the embryonic and neonatal skeleton, and in the bones of growing children. It is absent in normal adults but appears in the early hard callous following fracture.[252] In lamellar (mature) bone, collagen fibres are arranged parallel to each other to form multiple microscopic layers (lamellae) with osteocytes in between. Lamellar bone forms the structural component of cortical and cancellous bone.[252]

8.1.2.1 Cortical and cancellous bone

The majority (80%) of the adult skeleton is made up of cortical bone. Cortical bone is also known as 'compact bone', as it is made up of compact units (haversion systems) and haversian canals in which blood vessels, lymphatics, and nerves are surrounded by concentric lamellae of bone with osteocytes in between (Figure 8.1). Rings of trapped osteocytes intercommunicate *via* gap junctions within channels called canaliculi.[252] Cortical bone is well-suited to mechanical/structural/protective function as it is 80-90% calcified and therefore dense.[253] It is the major component of long bone and comprises the outside surface of all bones. It has a relatively low metabolic activity. Cancellous bone is synonymous with trabecular or 'spongy' bone. It is less dense (5-20% calcified) than cortical bone, and has a relatively high metabolic activity.[253] Cancellous bone is present in the internal meshwork of all bones, and at the end of tubular bones and vertebral bones. It is a honeycomb appearance microscopically, because it is laced with 'rod-like' trabeculae that greatly increase the surface area.[253] While it makes up only a quarter of the entire bone mass, it makes up two-thirds of the bone surface area. As metabolic activity only occurs on surface sites, it is the large surface area that confers the high metabolic activity, and therefore, it is here that the effects of metabolic disorders are first seen.

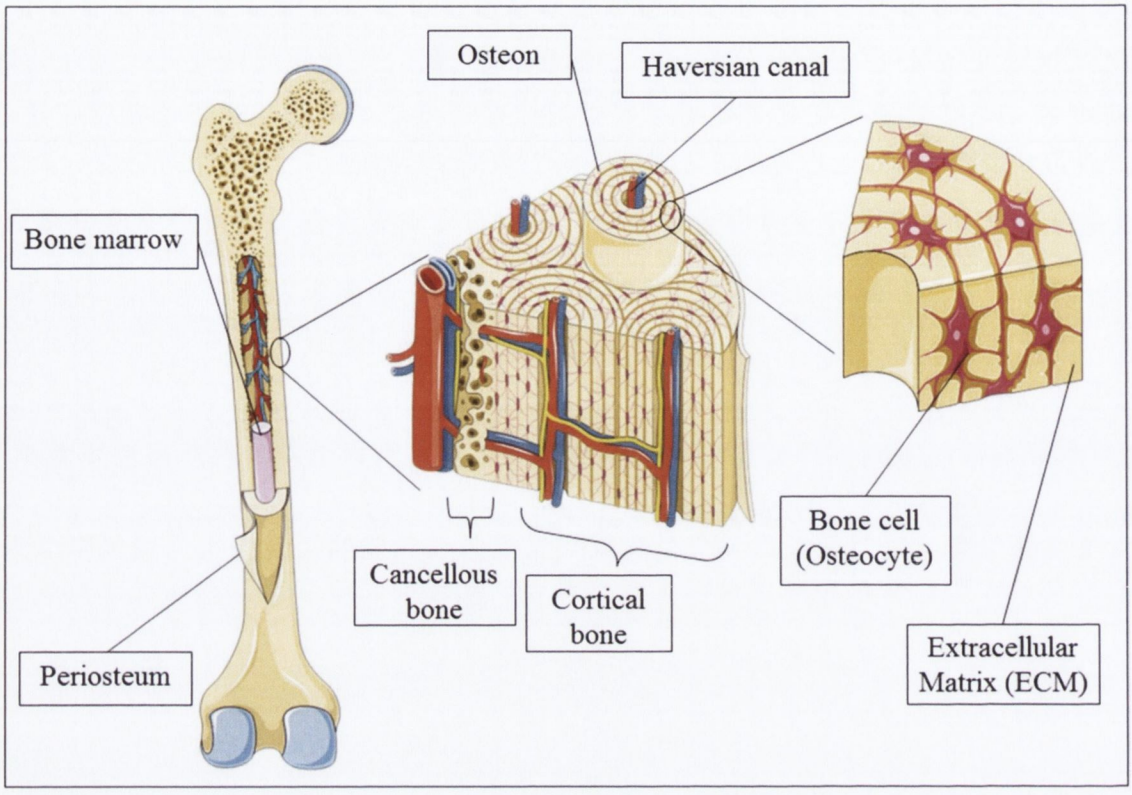


Figure 8.1 Schematic illustration of cancellous (trabecular) and cortical bone

From Le Meng Bao et al, InTech Open Access (2013). Accessed from: http://www.intechopen.com/books/regenerative-medicine-and-tissue-engineering/advances-in-bone-tissue-engineering[254]

8.1.2.2 Type 1 collagen

Type 1 collagen comprises more than 90% of the organic bone matrix. It has a triple helix structure formed from three chains, one of which has a high proportion of the amino acids proline and hydroxyproline. Type 1 collagen is synthesised as a precursor with large extension peptides on both the carboxy-terminal and amino-terminal ends, and these are cleaved during the secretion and fibril formation process (Figure 8.4). Type 1 collagen from bone contains hydroxylysylpyridinoline and lyslpyridinoline crosslinks. Crosslinks occur between lycine or hydroxylycine residues on the non-helical carboxy-terminal ends

(telopeptides), and the helical portions of an adjacent collagen.[253] Collagen is primarily responsible for the tensile strength of bone.[252]

8.1.2.3 Osteoprogenitor cells

Osteoprogenitor cells are mesenchymal stem cells that can undergo mitotic division and differentiate into osteoblasts. In mature bone that is not undergoing remodelling, osteoprotenitor cells are called bone lining cells.

8.1.2.4 Osteoblasts: bone forming cells

Osteoblasts develop from mesodermal progenitor cells which ultimately result in the production of matrix proteins (such as collagen 1) and regulators of matrix mineralisation (such as osteopontin and osteonectin).[255] Some osteoblasts develop into bone lining cells, but most develop into osteocytes. Once oseoblasts have produced bone matrix, they may die by apoptosis, a major mechanism which regulates their number and overall function. They also initiate degradation of bony tissue by activating osteoclasts.[255] Osteoblasts produce osteoprotegerin (OPG), which inhibits osteoclastogeneis and has a bone protection role.

8.1.2.5 Osteoclasts: bone resorbing cells

Osteoclasts are principal mediators of bone resorption, and are derived from monocyte precursors in marrow. Osteoclasts are multi-nucleated (typically 3-20 nuclei), have large numbers of mitochondria and lysosomes, and produce acid phosphatase.[252] By chemotactic stimuli, osteoclasts attach to specific regions on the cell surface (ruffled border) and release lysozyme which results in a shallow excavation (Howship lacunae). A low pH is produced below the ruffled border which dissolves the inorganic apatite crystals. Acidic proteolytic lysosomal enzymes then hydrolyse the organic matrix components.[252]

8.1.2.6 Osteocytes: mature bone cells

Osteocytes are essentially spent osteoblasts. They comprise about 90% of the bone cell population and interconnect with other cells *via* long cytoplasmic processes in the canaliculi.[252] They are sensitive to mechanical stimuli and communicate information regarding changes in stress and strain to the active osteoblasts. Under the influence of PTH they participate in bone resorption and calcium ion transport. Osteocytes are important in controlling calcium and phosphorus metabolism, responding to chemical stimuli such as PTH and calcitonin, and also to mechanical and electrical potential stimuli.[252]

8.1.3 Bone remodelling

The bone remodelling cycle refers to the coordinated interaction between osteoclasts and osteoblast to initially remove an area of bone (by osteoclastic action) and then replace the lost bone with a new matrix (by osteoblastic action) which then mineralises.[256] The bone remodelling cycle takes about 3-6 months, and the annual turnover rate is 4% for cortical bone and 25% for lamellar bone.[253] Bone metabolism is a dynamic and continuous remodelling process that is normally maintained in a tightly coupled balance between resorption of old, damaged, or injured bone, and formation of new bone. On a microscopic level, bone metabolism always occurs on the surface of bone at focused sites known as bone metabolism units (BMUs).[253] Global bone metabolism represents the cumulative behaviour of many BMUs so that alteration, imbalance or defects in either bone formation or resorption can cause rapid and substantial changes in bone integrity over time.[253] Whereas bone *modelling* only occurs in childhood (bone formation, without resorption), bone *remodelling* occurs throughout life. Both of these processes are vital to achieve strength and lightness for motility by strategically building bone in one location where it is needed and removing bone to avoid bulk where it is not needed.[257] In most situations, the amount of new bone formed is closely matched by the amount of old bone lost, but increasing age results in a small negative balance ultimately resulting in an age-related decline in BMD.[256] See Figure 8.2.

8.1.3.1 RANK, RANKL and OPG

Receptor activator of NF-κB (RANK) is a transmembrane protein belonging to the TNF receptor family and is expressed on the surface of cells of haemopoietic origin. RANK is the pivotal cytokine receptor for osteoclastogenisis, and leads to the activation of the transcription factor activator protein 1. RANK ligand (RANKL) is produced by osteoblasts and other mesenchymal cells, as well as by T- and B- lymphocytes.[257] RANKL interacts with its receptor RANK on osteoclast precursor cells and mature osteoclasts. The ligation of RANK with RANKL results in the commitment of macrophage precursor cells to the osteoclast lineage, and the activation of mature osteoclasts leading to increased bone resportion.[257] RANKL signalling is accelerated by IL-1, IL-6 and TNF-α. These mediators potently induce RANKL production by osteoblasts and are believed to directly contribute to the bone destruction process. The effects are counteracted by OPG, which is also produced by osteoblasts. It acts as a decoy receptor molecule that naturally binds to RANKL to inhibit osteoclast differentiation, blocking activation of the mature osteclasts. Thus OPG acts to reduce bone resorption.[255-257] The bone metabolism process under normal physiological conditions is schematically depicted in Figure 8.3.

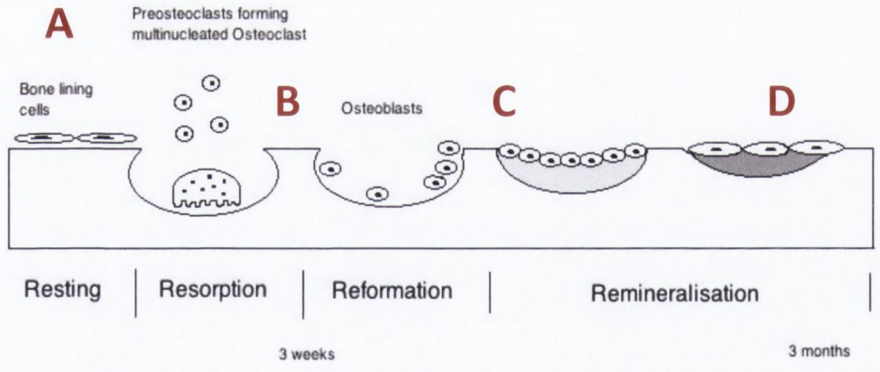


Figure 8.2 Schematic of the bone remodelling process

A Resting phase: bone surface is covered by a protective layer of bone lining cells

B Resorption phase: osteoclasts attach to the cell surface ('ruffled border') and release lysozyme which dissolves the mineral and matrix resulting in excavation of Howship lacunae

C Formation phase: osteoblasts lay down new bone matrix which then mineralises

D Quiescent phase after remodelling: spent osteoblasts develop into osteocytes

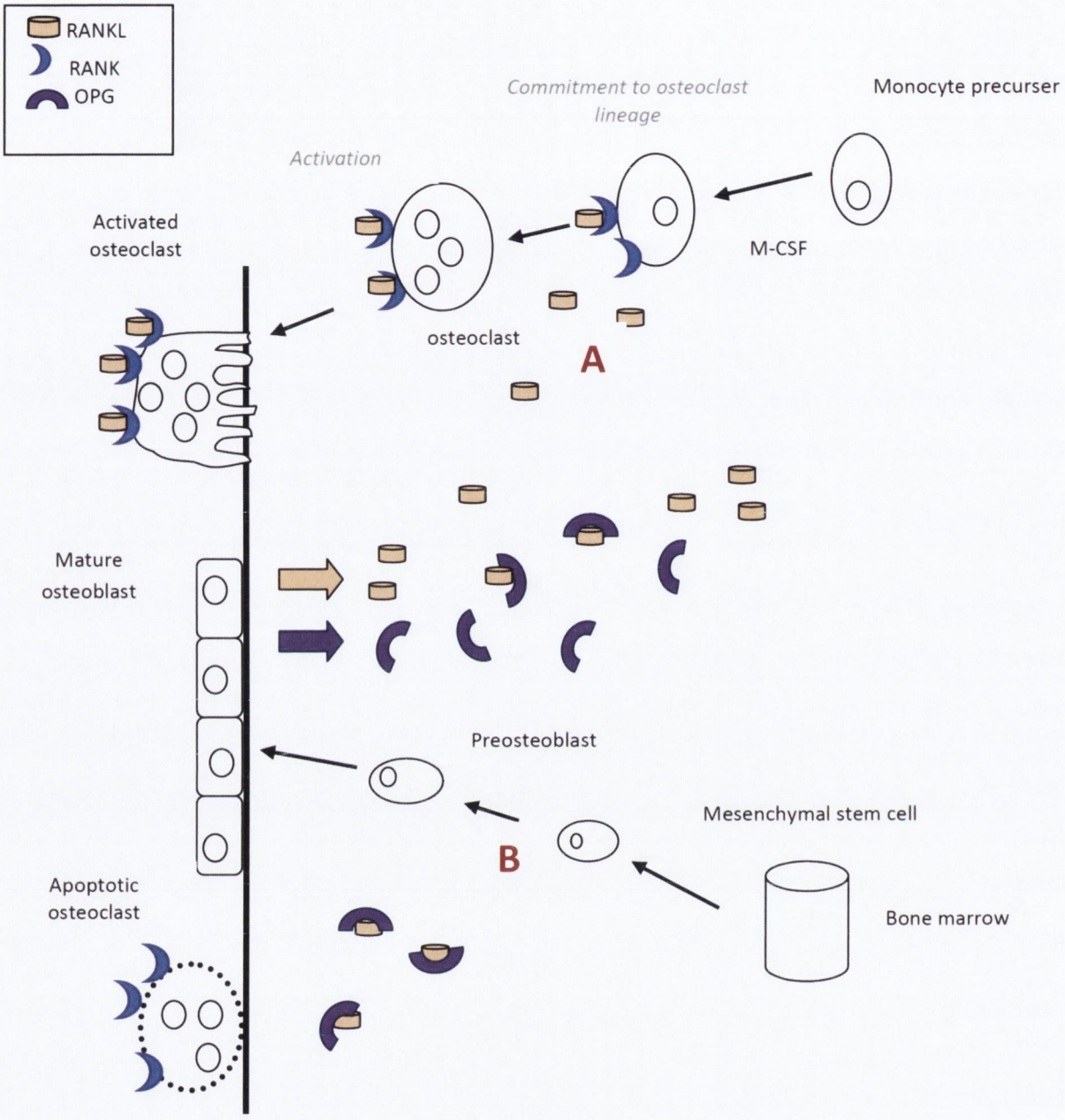


Figure 8.3 Schematic of bone metabolism under normal physiological conditions

A RANKL produced by osteoblasts, stromal cells or T-cells are required for differentiation of osteoclasts. The binding of RANK to RANKL commits monocyte precursor cells to the osteoclastic lineage

B Osteoblasts regulate osteoclast development by secreting OPG, a decoy receptor that competes with RANK for RANKL

8.1.4 The effect of inflammation

8.1.4.1 Pro-inflammatory cytokines

Pro-inflammatory cytokines IL-1, IL-6 and TNF-α stimulate bone resorption through osteoclast stimulation.[258] TNF-α also inhibits osteoblast response to PTH.[259] Osteoclast precursors as well as mature osteoclasts express receptors for IL-1, IL-6 and TNF-α. Additionally, pro-inflammatory cytokines suppress OPG expression, whilst enhancing that of RANKL, resulting in a marked increase in osteoclast formation and function.[248]

8.1.4.2 Inflammatory bone loss

Systemic osteoporosis and a high fracture rate occur in several inflammatory conditions, such as rheumatoid arthritis, chronic obstructive pulmonary disease, cystic fibrosis, systemic lupus erythematosus and psoriatic arthritis.[255] In the course of the inflammatory response, an array of cytokines are activated, including interferons, ILs and chemokines. Many of these affect the differentiation and function of osteoblasts and osteoclasts, and are therefore considered mediators of inflammation-associated osteoporosis.[255] Although osteoclast differentiation and activation is pivotally dependant on the presence of macrophage colony-stimulating factor (M-CSF) and RANKL, osteoclastogenesis is enhanced in the presence of IL-1, IL-6 and TNF-α, and while it is not known which of the pro-inflammatory cytokines serves as the major mediator of systemic bone loss, there is some evidence that IL-6 is key:[255]

- IL-6 is induced by IL-1 and TNF-α, is the most abundant cytokine, and has endocrine activity
- IL-6 can be induced in situations of stress independent of inflammation
- IL-6 mediates the activation of the hypothalamic-pituitary-adrenal axis by IL-1 and TNFα, which leads to the release of glucocorticoids that are capable of inducing bone loss
- Oestrogen deficiency causes up-regulation of IL-6. Oestrogen decreases RANKL expression and increases OPG production by osteoblasts

An increase in bone resorption should result in a stimulation of bone formation due to the normally tight coupling of bone resorption and formation. However, in many chronic inflammatory states, bone formation is suppressed or remains inappropriately normal relative to the degree of bone resorption. Thus the net effect is bone loss. This might be due to the direct affects of proinflammatory cytokines on osteoblasts, or due to an interruption of the signalling mechanisms that couple formation to resorption.[256]

8.1.4.3 Bone loss in IBD

The pathogenesis of osteopathy in IBD occurs secondary to a multifactorial (but still poorly understood) set of mechanisms. There are two major divisions: 1) osteopathy due to poor nutritional status and malabsorption, and 2) osteopathy due to systemic inflammation, specifically pro-inflammatory cytokines IL-1, IL-6 and TNF-α which affect bone directly. These two mechanisms may be interlinked, for example, inflammation and cytokine activity may contribute to abnormalities in intestinal and renal nutrient absorption.[257]

8.1.4.4 Bone loss in cystic fibrosis

In adult cystic fibrosis, a multifactorial aetiology for osteoporosis is likely, due to many of the same mechanisms as in chronic pancreatitis (including malabsorption, vitamin D insufficiency, and reduced physical activity). However, for patients with cystic fibrosis, there are additional factors to consider, including hypogonadism and glucocorticoid use. Additionally, the effects of the systemic inflammatory response to infections may affect osteoclast function and formation, through the release of cytokines including IL-6, TNF-α and RANKL. Bone turnover has previously been shown to be abnormal in patients with cystic fibrosis [258].

8.1.4.5 Serum hsCRP and bone loss

CRP is a protein named according to its ability to bind proteoglycan C of pneumococci. It is predominantly produced by the liver and increases by up to 100-fold during inflammation.[260] Il-1, Il-6 and TNF-α have been recognised as regulators of CRP production, and therefore

serum CRP may reflect the overall metabolic effect of pro-inflammatory cytokines. The high-sensitivity CRP assay (hs-CRP, also known as ultrasensitive CRP) allows for the assessment of CRP concentrations at the lower end of distribution.[260] Studies have reported a relationship between hsCRP and the progression of coronary heart disease,[261] and there is also an association between hsCRP and BMD and fracture risk in healthy individuals.[260, 262-263] No studies have examined the relationship between hsCRP and BMD in patients with chronic pancreatitis.

8.1.4.6 Inflammation in chronic pancreatitis

Inflammatory infiltrates (including T- and B-lymphocytes) are frequently observed within the pancreas in chronic pancreatitis, and pro-inflammatory cytokines closely related to the progression of acute pancreatitis are over-expressed in chronic pancreatitis and stimulate pancreatic fibrogenesis, indicating a pivotal role in the pathogenesis of pancreatitis.[264] The dynamics of serum / plasma concentration of IL-6, monocyte chemoattractant protein 1 (MCP-1), TGF-β1, IGF-1 and IGF-binding protein 3 have all been identified in the pathogenesis of chronic pancreatitis.[264] Furthermore, alcohol intake enhances the presence of pro-inflammatory cytokines. Increased levels of IL-6 have been demonstrated in patients with chronic pancreatitis compared to controls following ingestion of an alcohol bolus (40g of alcohol).[264]

8.1.5 Nutrition

8.1.5.1 Nutritional status

Chronic inflammatory conditions are frequently complicated by poor nutrition, either due to the direct catabolic affects of inflammation (resulting in reduced muscle mass) or due to reduced calorie intake. Additionally, malabsorption of nutrients in many GI conditions, particularly persistent calcium and vitamin D deficiencies, may negatively affect bone mineralisation which may independently increase the risk of bone fracture.

8.1.5.2 Calcium and phosphate metabolism

Ninety-nine percent of total body calcium is sequestered in bone, leaving just 1% circulating in extracellular fluid. Intracellular levels are negligible by comparison. Levels are very tightly regulated because calcium is important in neural transmission, muscle contraction and coagulation.[252] Calcium in absorbed from the duodenum by active transport (modulated by calcium-binding protein and adenosine triphosphate (ATP), and regulated by 1,25-OH D) and *via* passive transport in the jejunum. Dietary calcium deficiency leads to a progressive loss of BMD. Phosphate is a key component of bone mineral with 85% of the total body phosphate stores being found in bone. Phosphate functions as a buffer in enzyme solutions. Dietary intake is usually adequate.[252] Vitamin D is a naturally-occurring steroid and may be either ingested (rich dietary sources include oily fish such as salmon, mackerel, herring), or activated by cutaneous irradiation (sunlight). Vitamin D metabolites enhance calcium and phosphate absorption across the intestine *via* promotion of synthesis of a calcium-transporting protein and enhance osteoclastic resorption from bone, increasing serum calcium and phosphate. Vitamin D metabolites inhibit PTH release.[252] Ultra-violet light on the skin transforms 7-dehydrocholesterol to cholecalciferol, which is subsequently hydroxylated in the liver to 25-OH D (an inactive form and the most accurate indicator of body stores). 25-OH D is further metabolised in the kidney to 1,25-OH D (the active form) in response to a raised PTH, or a low serum, calcium / phosphate. PTH has numerous affects. It stimulates the activation of 25-OH D, increases the reabsorption of filtered calcium in the kidneys, promotes urinary excretion of phosphate, and stimulates osteoclastic (bone resorption) activity. Vitamin D deficiency results in an increase in PTH secretion. PTH receptors are expressed on osteoblasts and persistent PTH signalling results in an increase in RANKL expression on osteoblasts. Increased RANKL expression results in an increase in bone resorption.[256]

8.1.6 Assessing diseases of bone

There are several methods for assessing diseases of bone. Histomorphometry provides critical information in the activation of BMUs and the rate of bone turnover. However, this technique is limited to a biopsy of the iliac crest in adults and therefore accuracy at other

sites may be compromised. Further limitations were discussed in Section 7.2.4.6 (Chapter 7). Monitoring calcium accretion rates can be useful for the quantitative assessment of bone loss during menopause, but may not be accurate in other groups. BMD measurement is an important tool, and BMD *via* DXA is the most useful method with high accuracy and precision. Clinically, this is an important tool; however, the technology is limited as the efficacy of any intervention cannot be measured for at least 2-3 years. Therefore, a more immediate measure of bone status is required. Biochemical markers of bone metabolism (bone turnover markers, BTMs) can provide a more immediate 'real-time' assessment of bone formation, resorption and turnover.[253] BTMs provide an easy and non-invasive method of assessing skeletal turnover.

8.1.7 Markers of bone metabolism

BTMs may be of some value for predicting bone loss in individual patients. In a systematic review, Chopin *et al* found that there was a moderate relationship between levels of bone metabolism and bone loss in peri- and post-menopausal women; however, the relationship appears to be variable. Nevertheless, high levels of BTMs (>2 SD) can identify patients with higher risk of increased bone loss (especially if bone turnover markers are high in repeated sampling).[265] Elevated BTMs (most consistently bone resportion markers) are associated with an increased risk of hip and non-vertebrae fracture and may be considered an independent risk factor for future fracture and could be used in conjunction with age and other risk factors, including BMD. This is especially true for long-term fracture risk (5-10 years).[265] Rather than looking at any one method of assessment in isolation, the combination of a biochemical marker along with BMD may be a much more powerful predictor of fracture than BMD alone.[266-267]

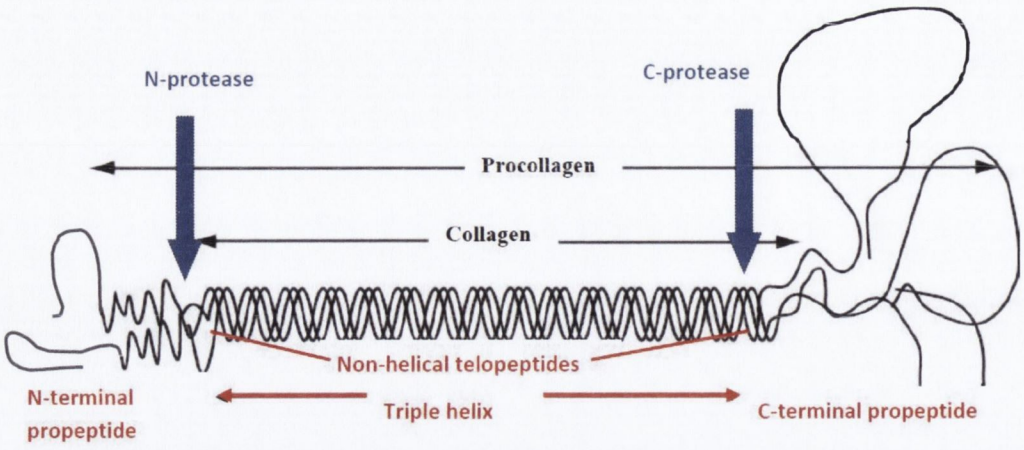


Figure 8.4 Schematic illustration of type 1 collagen with amino-terminal (N-terminal) and carboxy-terminal (C-terminal) ends

The N- and C- terminal propeptides are cleaved by specific proteases and are thus released in to the circulation where they may be measured

8.1.7.1 Procollagen 1 animoterminal propeptide: P1NP

As described in Section 8.1.2.2, type 1 collagen is an important component of bone matrix and is synthesised by osteoblasts as a larger precursor protein (procollagen 1) during bone formation. The carboxy- and amino-terminal ends of procollagen 1 are enzymatically 'clipped' during processing, prior to incorporation of type 1 collagen into the bone matrix. This cleavage yields two relatively large extension peptides: procollagen 1 carboxy-terminal propeptide (P1CP) and procollagen 1 animo-terminal propeptide (P1NP) (Figure 8.4). As type 1 collagen comprises the majority of matrix protein produced during bone formation, measurement of P1CP and P1NP fragments in circulation should be good markers of bone formation.[253, 268]

8.1.7.2 Osteocalcin

OC is one of the most abundant non-collageneous proteins in bone matrix. It is also produced by the osteoblasts during bone formation, and some proportion finds its way into

the extracellular compartment where it can be measured.[268] OC binds to hydroxyapatite and much of it is deposited in the bone matrix.[269] OC is therefore a later marker of osteoblast differentiation as it appears in the bone mineralisation stage.[270] OC synthesis is vitamin K-dependant.[253]

8.1.7.3 Serum carboxy-terminal telopeptide of type 1 collagen: CTX-1

Carboxy-terminal telopeptide of type 1 collagen (CTX-1) fragments are released into circulation as a result of the osteoclast-mediated degradation of type 1 collagen during the normal bone resorption process.[253] In elevated bone resorption (for physiological or pathological reasons), type 1 collagen degradation is increased, and there is a corresponding rise in the level of collagen fragments in the serum. Therefore, by measuring these markers of bone resorption, osteoclast activity can be determined. The β-isomerised C-terminal telopeptides (β-CTX) are particularly relevant, as they are highly specific for the degradation of the type 1 collagen dominant in bone.[271] From a technical viewpoint, serum CTX-1 has several advantages over urinary markers of type 1 collagen degradation (such as urinary CTX, urinary NTX and urinary total deoxypyridoline): it does not require measurement of urinary creatinine; it is widely available and has both short-term and long-term within-subject variability (approximately twice lower than urinary markers).[265]

8.1.8 Other factors affecting bone homeostasis

Hypogonadism is known to contribute to decreased BMD in several conditions, including IBD and cystic fibrosis. Children with IBD often suffer from growth retardation and pubertal delay due to the combined effects of glucocorticoids, poor nutrition and proinflammatory cytokines on the growth hormone/ IGF-1 axis and the gonadal axis at both systemic and local levels.[272] The AGA in its recommendations for bone health in GI conditions listed hypogonadism as a risk factor for osteoporosis requiring a DXA scan to assess BMD.[111] Although hypogonadism is not known as a feature of chronic pancreatitis, sex hormones were considered in this study in order to out rule this cause.

Similarly, as hyperthyroidism is a known cause of osteoporosis, this should be out ruled as a contributing factor in chronic pancreatitis. Hyperthyroidism results in accelerated bone resorption and formation, with a net effect of bone loss and high bone turnover osteoporosis.[273]

IGF-1 is mainly synthesised by the liver and is responsible for the growth promoting effects of growth hormone in various tissues.[274] IGF-1 stimulates bone formation by increasing the protein content of osteoid. This is achieved by promoting preosteoblastic proliferation and by decreasing collagen degradation, as well as increasing protein synthesis.[253] A decline in serum IGF-1 may be an important mechanism for the development of osteoporosis with advancing age, and IGF-1 may be an important serum marker for low BMD, particularly in post-menopausal women.[274]

8.1.9 Study rationale

There is considerable evidence that patients with chronic pancreatitis have an increased risk for osteoporosis, including data from the prevalence study described in Chapter 7, which was further strengthened by data from the systematic review and meta-analysis in the same chapter. There is also evidence that those with chronic pancreatitis are at a higher risk than normal for low-trauma fractures.[239] However, the pathogenesis of low BMD in chronic pancreatitis has not been characterised, and therefore the aetiology of osteoporosis is unknown. Similarly, bone metabolism has not been well-studied in chronic pancreatitis and therefore, it is not known if the bone demineralisation process is a consequence of increased bone resorption, or decreased bone formation. BTMs have the potential to identify those at most risk of fracture, in conjunction with assessment of BMD, and may also be important in monitoring osteoporosis therapy. Many BTMs exist; however, in a position paper on BTMs for the prediction of fracture risk and the monitoring of osteoporosis therapy, the Bone Markers Standards Working Group, whilst recognising that there is not yet a gold standard or perfect BTM, recommended serum CTX-1 as the reference standard for bone resorption and serum P1NP as the reference standard for bone formation.[268] Therefore, both P1NP and CTX-1 were selected for analysis in this study. OC was also analysed as an additional marker of bone formation. Chronic pancreatitis is an inflammatory condition. However, the relationship

between inflammation and bone metabolism has not been investigated. Therefore, this study also sought to examine the relationship between BMD, BTMs and sensitive serum markers of inflammation.

8.1.10 Study objectives

The aims of this study were to assess bone metabolism by measurement of BTMs and BMD in patients with chronic pancreatitis compared to matched controls, and to investigate the relationship between inflammatory markers and bone metabolism.

8.2 Methods

8.2.1 Study description

In this prospective case-controlled study, patients with chronic pancreatitis were recruited from either The Centre for Pancreatico-Biliary Disease, Tallaght Hospital, Dublin or from The Hepato-Biliary Surgical Service at St Vincent's University Hospital, Dublin.

8.2.2 Recruitment

Prospective adult patients of both genders were identified from an existing departmental database and invited to attend by letter (Appendix N), or recruited from the specialist pancreatic clinic. All patients were recruited from the outpatient setting, or were inpatients not in an acute inflammatory response. The control group were matched for age, sex and education level. They comprised 29 subjects who volunteered following advertisement. Inclusion criteria for patients were as follows:

- Diagnosis of chronic pancreatitis (documented by the medical team according to accepted radiological/ clinical criteria)
- Willing to participate (informed consent)
- Adult, >18 years

Prior to recruitment, patients and controls underwent 'subject suitability screening'. Subjects were not eligible for participation of any of the following applied: subject had been recruited to phase 1 (Chapter 7); subject was on medication which may affect bone turnover; subject had a history of major GI resection; subject had a history of malabsorptive condition (e.g. coeliac disease, IBD); Subject had cystic fibrosis or pancreatic cancer; subject was pregnant, or subject had a prognosis of <6 months (Appendix O). The recruitment process and inclusion/ exclusion process is illustrated in Figure 8.5. Upon inclusion in the study, subjects were invited to attend an out-patients appointment and a data collection form was completed for each participant (Appendix P).

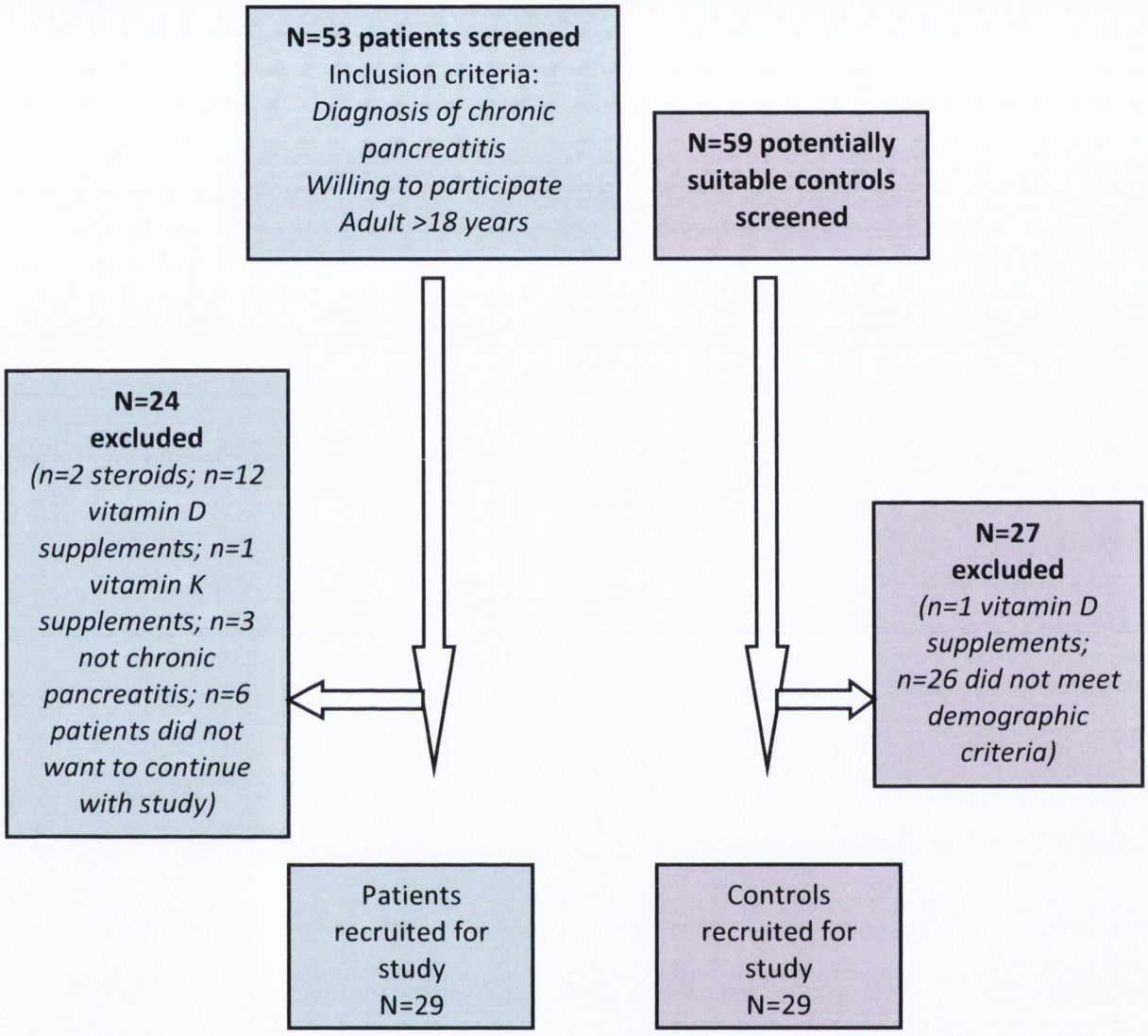


Figure 8.5 Recruitment process for patients and controls

8.2.3 Assessment

8.2.3.1 Anthropometry

Weight was taken to the nearest 0.1Kg with subjects wearing light clothes and no shoes. Height was taken to the nearest 0.1M without shoes. BMI was calculated from these measures as Kg/M^2. See Chapter 4.

8.2.3.2 Biochemistry

Following an overnight fast, blood samples were drawn by venopuncture between 0800 and 0900 hours by a trained phlebotomist (at Tallaght Hospital Phlebotomy Department). For BTM assays, serum was separated within 1 hour and aliquoted into plastic 13x75mm tubes (OC 0.5ml, P1NP 0.5ml, CTX-1 0.6ml). They were stored at -20° Celsius (C) prior to transporting to the Metabolism Laboratory at SVUH according to protocol.

8.2.3.2.1 Bone metabolism bloods

Bone formation markers OC, P1NP and CTX-1 were measured in serum taking in the fasting state using commercially-available kits. P1NP was measured by competitive radioimmunoassay (Orion Diagnostica, Espoo, Finland) with intra- and inter-assay coefficient of variation (CV) of <5% and <7% respectively. OC was measured by sandwich immunoradiometric assay (Cis Bio International, Bagnols/Ceze, France) with intra- and inter-assay CVs of <2% and <6% respectively. CTX-1 was measured using a solid-phase 2-site chemiluminescent enzyme-labelled immunometric assay (Roche Diagnostics, GnbH, Mannheim, Germany), with intra- and inter-assay CVs of < 2% and <4% respectively.

8.2.3.2.2 Inflammatory markers

Serum TNF-α was measured by solid-phase enzyme-linked immunosorbant assay (ELISA) using the quantitative sandwich immunoassay technique (Quantikine Human TNF-α Immunoassay, R&D Systems Inc., USA). The intra- and inter-assay CV were <6% and <8% respectively. Expected values for normal were <15 pg /ml based on values for 40 apparently

healthy controls (manufacturer's information). Serum IL-6 was measured by solid-phase ELISA using the quantitative sandwich immunoassay technique (Quantikine Human IL-6 Immunoassay, R&D Systems Inc., MN, USA). The intra- and inter-assay CV were <5% and <7% respectively. Expected values for normal were <3 pg / ml based on values for 33/40 apparently healthy controls (manufacturer's information). hs-CRP was measured by particle-enhanced immunoturbidometric assay.

8.2.3.2.3 Other bloods

Endocrine axes were investigated by measurement of follicular-stimulating hormone (FSH), luteinising hormone (LH), oestradiol, and testosterone by electrochemiluminescent immunoassay (Roche Diagnositics, Mannheim, Germany) in subjects of the appropriate sex. Serum 25-OH D was measured by liquid chromatography-tandem mass spectrometry (in the Biochemistry Department of St. James Hospital, Dublin) and PTH was measured using solid-phase 2-site chemiluminescent enzyme-labelled immunometric assay. IGF-1 was measured by chemiluminescent assay using the IDS iSYS instrument (IDS France, Pouilly-en Auxois, France). A gender- and age-specific reference range was used for IGF-1 values. Thyroid stimulating hormone (TSH) and free T4 were measured by electrochemiluminescent immunoassay (Roche Diagnositics, Mannheim, Germany). Details on biochemical assays and reference ranges are provided in Chapter 4.

8.2.3.3 BMD

BMD was measured by a radiographer by DXA using a Lunar Prodigy Advance Densiometer, software version 11.4 (GE Healthcare, GE Medical Systems, Belgium). The measurement sites selected were the lumbar spine L1 – L4, and the femoral neck (right and total). For all sites, BMD (g/cm^2) was reported as well as T-scores and Z-scores (see Chapter 4). Diagnostic categories according to the WHO report relating to normal or low BMD values were used (see Chapter 4).[128] All female subjects were asked about their menstrual status, and DXA was only performed from days 1-10 of their menstrual cycle in case of pregnancy.

8.2.3.4 Other

Alcohol intake was recorded: units of alcohol per day or per week; type of alcohol consumed; frequency of consumption. Units of alcohol were calculated. Smoking status was recorded: current/ex/never. For ex- or current-smokers, the number of cigarettes per day was recorded, over a given number of years. Pack year history was subsequently calculated. Date of birth, gender and education level (highest education level completed) were recorded. Data on chronic pancreatitis aetiology, symptoms of PEI, and DM, were also recorded.

8.2.3.4 Ethics

Ethical approval was awarded by the joint Tallaght Hospital/ St James Hospital Ethics Committee. All study participants gave informed consent prior to inclusion.

8.2.4 Statistics

For continuous variables, results were presented as mean and SD, and for non-continuous variables, results were presented as frequency and percentage. Before comparing groups, tests of data normality were done using the Anderson-Darling normality test. Student's T-test was used to compare normally-distributed (parametric) data. To compare group means, ANOVA was done, and where appropriate, *post-hoc* analysis was performed using Tukey. Where distribution of data did not follow a normal distribution in the preliminary analysis, comparison between groups was done by the non-parametric Mann-Whitney U-test. For multivariable analysis, multiple stepwise regression was performed. All variables showing independent significant associations by univariate/bivariate analysis were entered into a multiple regression model for further analysis. Bivariate correlation was done using Pearson's correlation and χ^2 analysis was performed for categorical variables. For data with outlier(s) considerably skewing the distribution, a logarithmic transformation was calculated and the data re-analysed. In some cases due to rounding, % values do not add up to 100. For all tests, a P - value of < 0.05 was considered significant. Data were analysed using Minitab, version 15.1 (State College, PA, USA).

8.3 Results

8.3.1 Demographics

Between April 2012 and April 2013, 58 subjects were recruited; 29 chronic pancreatitis patients and 29 controls (Table 8.1). Of the patients, 17 were male (58.6%) and 12 (41.4%) were female, with a mean (SD) age of 44.3 (12.2) years. Most patients had an alcohol aetiology (55.2%), followed by idiopathic (20.7%) and gallstones (17.3%). Most patients (86.2%) had completed 1st level education or less, while (13.7%) had completed second level or higher. A quarter of patients (24.1%) were in employment, a fifth (20.7%) were homemakers, while over half (55.1%) were not in employment. Patients and controls were matched for age, sex and education level completed, and there was no significant difference between the groups for these indices (P = 0.614, P = 1.0, P = 0.888 respectively).

Table 8.1 Demographic details for patients and controls

	Patient	Control	95% CI	*P*
Age in years , mean (SD)	44.3 (12.3)	45.8 (9.8)	-4.4, 7.6	0.614$^{\mu}$
Sex, female/male	12/17	12/17	-	1.0§
Post-menopausal women n(%)	5 (17.2)	5 (17.2)	-	1.0§
Completed ≥2nd level education, n (%)	4 (13.7)	4 (13.7)	-	0.888§
BMI Kg/M^2, mean (SD)	25.2 (5.1)	27.3 (3.7)	-0.32, 4.4	0.09$^{\mu}$
Smoking				
Current, n(%)	20 (69.0)	5 (17.2)	-	
Ex, n(%)	3 (10.3)	5 (17.2)	-	<0.0001§*
Never, n(%)	6 (20.7)	19 (65.5)	-	
Pack year history$^{\#}$, mean (SD)	16.9 (14)	6.4 (11.9)	-	-
Pack year history$^{\#}$, median	15 (25.35)	0 (8)	-20, -2.8	0.0019$^{\beta}$*
Alcohol				
Current, n(%)	4 (13.8)	28 (96.6)	-	-
Ex, n(%)	23 (79.3)	0	-	<0.0001§*
Never, n(%)	2 (6.9)	1 (3.4)	-	-
Alcohol intake units, mean (SD)	0.945 (3.8)	11.7 (10.5)	-	<0.0001$^{\mu}$*
Alcohol intake units, range	0-20	0-42	-	-

* Statistically significant, μ Student's T-test, § Pearson's χ^2 test, β Mann Whitney U-test, # mean pack year history among current or ex-smokers

8.3.2 BMI, smoking, alcohol, and DM

Patients had lower BMI scores than controls, but this was not statistically significant (P = 0.09). Sixty-nine percent of patients (n = 20) reported being current smokers, and a fifth of the group (n = 6, 20.7%) reported never having smoked. These rates were higher than among controls: five controls (17.2%) were current smokers and two-thirds (n = 19, 65.5%) were never-smokers ($P < 0.0001$). Patients were also heavier smokers than controls based on pack year history ($P = 0.001$). Regarding alcohol intake, 4 patients (13.8%) and 28 controls (96.6%) were current alcohol drinkers, with 23 patients (79.3%) and no controls being ex-drinkers ($P < 0.0001$). A third of patients had pancreatogenic DM and 6 (21.4%) were insulin-controlled. Four patients reported symptoms consistent with fat malabsorption.

8.3.3 BMD

Significantly more patients had osteoporosis ($P = 0.019$) and overall osteopathy ($P = 0.05$) than controls (Table 8.3). BMD was lower among patients at the L1:L4 lumbar vertebrae (P = 0.014) and right femoral neck ($P = 0.029$), but not at the total hip. BMD T-scores were lower for patients at all areas ($P < 0.05$ for all) (Table 8.2).

There was no effect of having DM or not on BMD, nor did those reporting exocrine symptoms have lower BMD. There was no relationship between BMD and BMI ($P = 0.753$), age ($P = 0.579$) or sex ($P = 0.068$) (all for total hip). As the value for sex was approaching significance, the effect was evaluated for all subjects (patients and controls), and overall, men had higher BMD than women (95% CI 0.025, 0.2315) ($P = 0.016$). This was also true for the right femoral neck ($P = 0.011$), but not L1:L4 ($P = 0.099$).

Table 8.2 BMD for patients and controls

	Patients		Controls		95% CI	P
	BMD, mean (SD)	***T-score, mean (SD)#***	***BMD, mean (SD)***	***T-score, mean (SD)#***		
Lumbar vertebrae L1:L4	1.094 (0.165)	-0.91 (1.3)	1.212 (0.189)	-0.07 (1.3)	0.025, 0.217	0.014μ*
Right femoral neck	0.926 (0.157)	-0.85 (1.2)	1.009 (0.12)	-0.19 (0.9)	0.009, 0.156	0.029 μ*
Total hip	0.955 (0.136)	-0.78 (1.0)	1.005 (0.222)	-0.09 (0.8)	-0.005, 0.147	0.307μ

* Statistically significant, μ Student's T-test, # Student's T-test for difference between T-scores was <0.05 in all cases

8.3.4 Bone-related biochemistry

Serum levels of P1NP, OC and CTX-1 are presented in Table 8.3 and illustrated graphically in Figure 8.6. Mean levels of P1NP were 61.2 (30.2) ug/L for patients and 41.6 (11.8) ug/L for controls. Comparing median values, patients had higher levels of PINP than controls (P = 0.0068), and over a quarter of patients had raised levels (compared to 1 control) (P = 0.006). Four controls had low levels of P1NP, while only 1 patient had levels lower than the reference range. OC levels among patients (13.7 (4.5) ug/L) were higher than that of controls (11.5 (3.0) ug/L) (P = 0.033), however, only one patient had levels above the reference range (no controls had levels above the reference range). Eight controls (27.6%) had low levels of OC, compared to five patients (17.2%). There was no statistical difference between median serum levels of CTX-1 between patients (0.419 ug/L) and controls (0.38 ug/L), however, seven patients (24.1%) had levels above the reference range, compared to only one control (P = 0.022). Neither patients nor controls had low levels of CTX-1. For patients, there were substantial and statistically significant relationships between the various BTMs. For controls, the relationships were less strong, but still moderate for all BTMs. Figure 8.7 illustrates the statistically significant direct correlations between specific BTMs for patients and controls.

Table 8.3 Bone-related biochemistry and BMD levels for patients and controls

	Patients	Controls	95% CI	*P*
Vitamin D and PTH				
25-OH D nmol/L, mean (SD)	37.0 (25.4)	50.8 (23.5)	-	-
25-OH D nmol/L, median (IQR)	31.0 (39.5)	42.0 (32.5)	-24.0, -3.0	0.0126^{β}*
25-OH D <25 nmol/L, n (%)	13 (44.8)	0		$<0.0001^{\S}$*
25-OH D <50 nmol/L, n(%)	20 (68.9)	18 (62.1)	-	$0.401^{\S}$
PTH pg/ml, mean (SD)	47.1 (19.4)	46.3 (14.0)	-9.7, 8.2	0.867^{μ}
BTMs				
P1NP ug/L , mean (SD)	61.2 (30.2)	41.6 (11.8)	-	-
P1NP ug/L, median (IQR)	52.5 (33.2)	41.7 (17.35)	2.8, 22.5	0.0068^{β}*
Raised P1NP, n(%)	8 (27.6)	0	-	$0.006^{\S}$ *
OC ug/L mean (SD)	13.7 (4.5)	11.5 (3.0)	-4.21, -0.19	0.033^{μ}*
Raised OC, n(%)	1 (3.4)	0	-	#
CTX-1 ug/L, mean (SD)	0.48 (0.24)	0.41 (0.12)	-	-
CTX-1 ug/L, median	0.419 (0.30)	0.386 (0.25)	-0.064, 0.126	0.559^{β}
Raised CTX-1, n(%)	7 (24.1)	1 (3.4)	-	$0.016^{\S}$*
BMD				
Osteoporosis, n(%)	9 (31)	2 (6.9)		
Osteopenia, n(%)	13 (44.8)	15 (51.7)		$0.05^{\S}$*
Normal BMD, n(%)	7 (24.1)	12 (41.4)		

* Statistically significant, μ Student's T-test, § Pearson's χ^2 test, β Mann Whitney U-test,

Not amenable to χ^2 testing due to small cell numbers

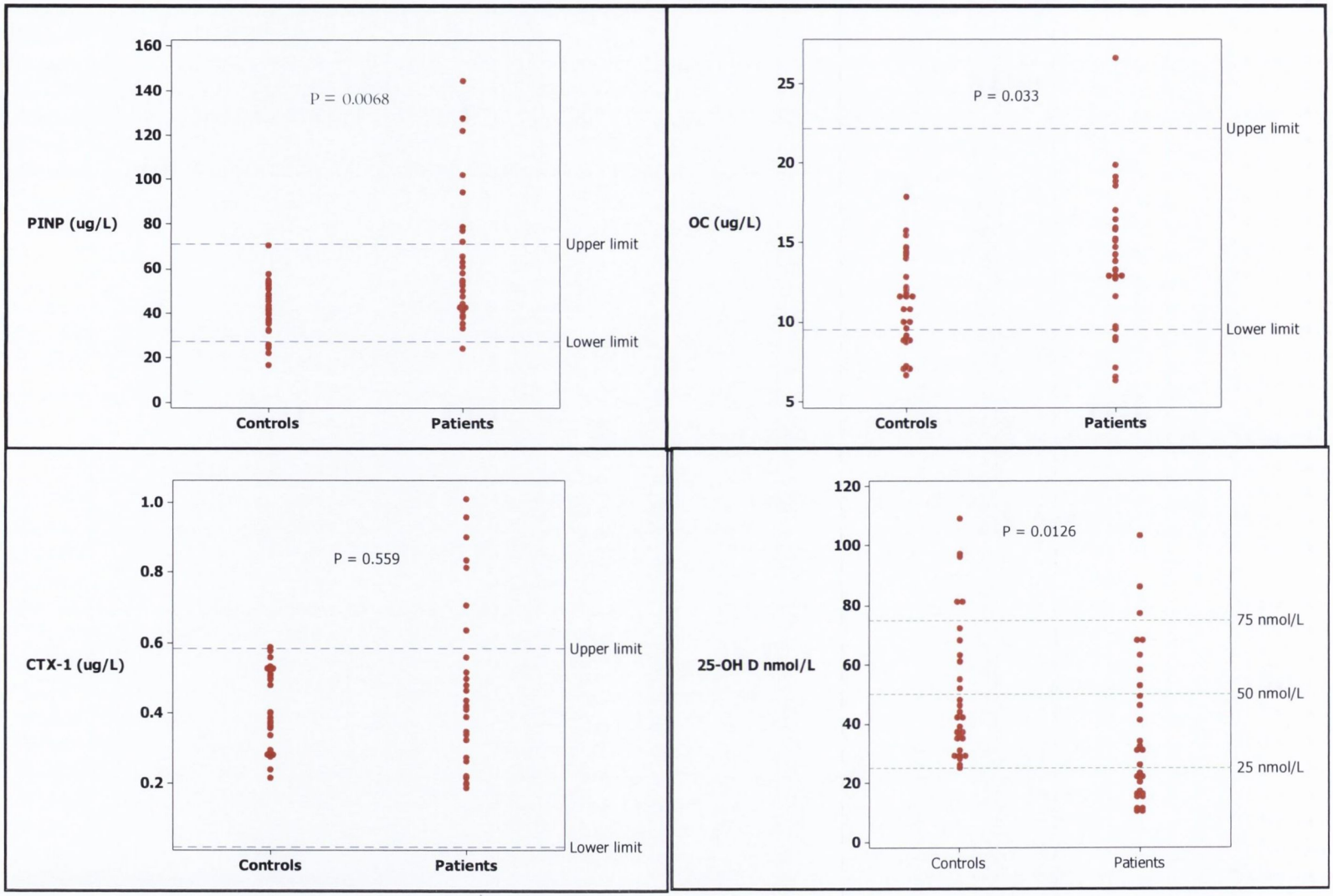


Figure 8.6 Individual value plots comparing levels of P1NP, OC, CTX-1 and 25 OH D between patients and controls

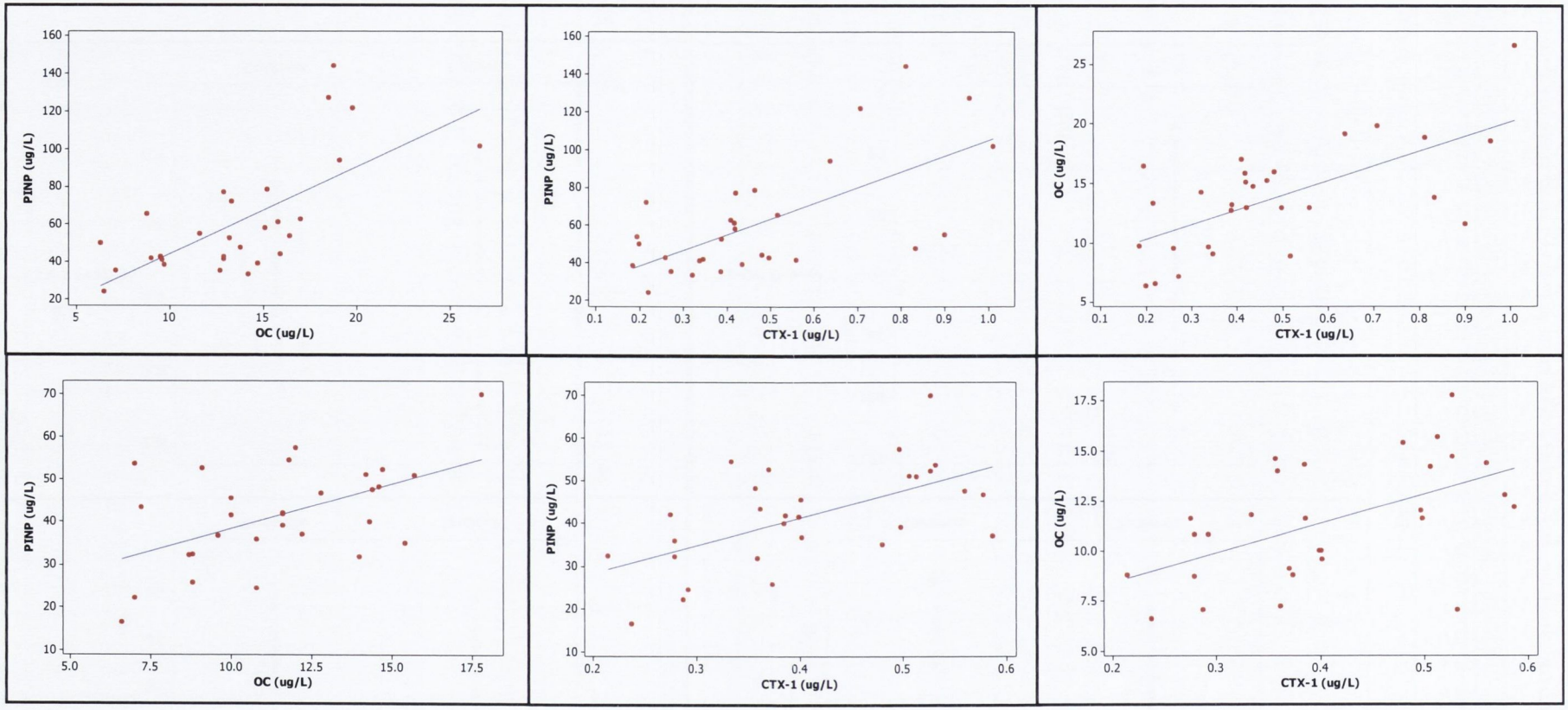


Figure 8.7 Scatter plots showing correlation between serum levels of BTMs

A. P1NP and OC among patients, R = 0.695, $P < 0.0001$; B. P1NP and CTX-1 among patients, R = 0.656, $P < 0.0001$; C. OC and CTX-1 among patients, R = 0.651, $P < 0.0001$; D. P1NP and OC among controls, R = 0.527, $P = 0.003$; E. P1NP and CTX-1 among controls, R = 0.597, $P = 0.001$; F. OC and CTX-1 among controls, R = 0.54, $P = 0.002$

8.3.5 Inflammatory markers

The median hsCRP level among patients was 3.15 mg/L, which was significantly higher than that of controls (0.9 mg/L) (P = 0.0013) (Table 8.4). Patient IL-6 levels were higher than controls, but fell outside of statistical significance (P = 0.057); IL-6 levels were affected by the failure to detect levels of less than 3 pg/ml (high-sensitivity region). Similarly, the TNF-α assay did not detect levels <15 pg/ml; no subjects had levels above this value. Twice as many patients (n = 24) had at least one raised inflammatory markers (hsCRP or IL-6) as did controls (n = 12).

Table 8.4 Inflammatory markers, sex hormones and thyroid function tests for patients and controls

	Patients	Controls	95% CI	*P*
Inflammatory markers				
hs-CRP mg/L, median (IQR)	3.15 (1.3-7.75)	0.9 (0.5-2.15)	0.6, 3.3	0.0013$^{\beta}$*
hs-CRP mg/L, range	0.1 – 158.4	0.1 – 7.1	-	-
IL-6 pg/ml, mean (SD)$^{\#}$	5.61 (5.23)	3.58 (1.82)	-0.06, 1.82	0.057$^{\mu}$
IL-6 n(%) above reference	10 (34.5)	4 (13.8)	-	0.066§
TNF-α n(%) above reference	0	0	-	-
Other measures				
IGF nmol/L, mean (SD)	20.57 (6.37)	21.34 (6.72)	-4.63, 3.08	0.688$^{\mu}$
Sex hormones				
FSH U/L, median (IQR)	6.0 (9.0)	7.0 (14)	-3.0, 2.0	0.61$^{\beta}$
LH U/L, median (IQR)	7.0 (9.5)	6.0 (9.0)	-2.0, 3.0	0.95$^{\beta}$
Oestradiol pmol/L, median(IQR)	177.0 (506)	84.0 (361.5)	-107.9, 394.9	0.9$^{\beta}$
Testosterone nmol/L, mean (SD)	18.54 (9.94)	17.2 (5.1)	-4.26, 6.97	0.624$^{\mu}$
Thyroid function tests				
TSH mU/L, mean (SD)	2.51 (1.82)	3.55 (2.94)	-	-
TSH mU/L, median (IQR)	1.9 (2.1)	2.8 (2.2)	-1.57, 0.13	0.063$^{\beta}$
Free T4 pmol/L, mean (SD)	16.57 (2.7)	15.27 (2.38)	-0.041, 2.64	0.57$^{\mu}$

* Statistically significant, μ Student's T-test, β Mann Whitney U-test

$^{\#}$Levels <3.0 pg/ml not detected

8.3.5.1 hsCRP: log-transformation

As the data for hsCRP were affected by a significant outlier (Figure 8.8) and were not normally distributed, a logarithmic transformation was done.[275] The Anderson-Darling test showed that the data followed a normal distribution following logarithmic transformation (Figure 8.9).

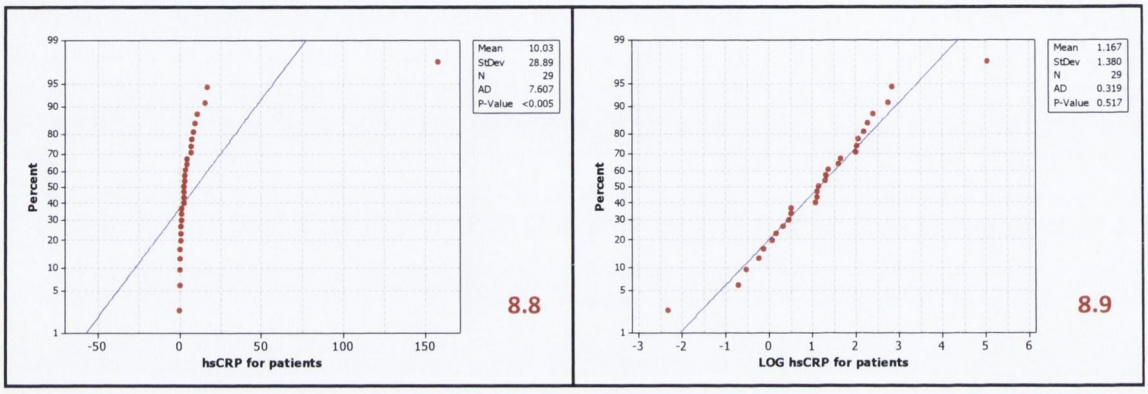


Figure 8.8 Normal probability plot for patient hsCRP values showing non-normally-distributed data (Anderson-Darling $P < 0.005$)

Figure 8.9 Normal probability plot for patient hsCRP values following logarithmic transformation showing normally-distributed data (Anderson-Darling $P = 0.517$)

8.3.6 Sex hormones, thyroid function and IGF-1

There was no statistical difference between levels of the sex hormones measured (FSH, LH, oestradiol, testosterone) between patients and controls ($P > 0.05$ for all) (Table 8.3). There was no significant difference between mean levels of TSH or free T4 between patients and controls, nor was there any correlation between TSH and BMD for either patients ($P = 0.43$) or controls ($P = 0.351$). Similarly, serum IGF-1 levels did not differ between patients and controls ($P = 0.688$), nor was there any relationship between IGF-1 and BMD for patients at any site.

8.3.7 Serum 25-OH D

8.3.7.1 25-OH D and PTH

The median 25-OH D levels for patients was significantly lower than that of controls (P = 0.0126), and the proportion of patients with 25-OH D levels below 25 nmol/L was significantly higher among patients than controls (P < 0.0001), although there was no difference for <50 nmol/L. PTH was not different between the 2 study groups. For patients, 25-OH D and PTH were moderately (inversely) correlated, R = -0.434, P = 0.019. Serum 25-OH D did not correlate with any of the BTMs: P1NP (P = 0.059), OC (P = 0.395), CTX-1 (P = 0.274).

8.3.8 Subgroup analysis

8.3.8.1 Factors associated with serum 25-OH D

25-OH D values were divided into two groups (<50 nmol/L and >50 nmol/L) for univariate analysis. Among patients, serum 25-OH D of <50 nmol/L was associated with high P1NP levels (P = 0.022), but not CTX-1 or OC. This group of patients with serum vitamin D levels <50 nmol/L were also heavier smokers (P = 0.039). For controls, there was no relationship between vitamin D and BTMs, but there was also a relationship between low vitamin D and heavy smoking (P = 0.016).

Multiple (linear) regression was performed to identify factors independently associated with serum 25-OH D. For patients, age was positively associated with 25-OH D (P = 0.024), while smoking and PTH levels both maintained an inverse association in the regression model (P = 00.03, P = 0.029, respectively). For controls, there were no such independently associated factors using the same statistical test, although an inverse association between smoking and 25-OH D fell just outside of significance (P = 0.052). Tables 8.5 and 8.6 display the data, along with factors not significant in the models, including BTMs and inflammatory markers.

Table 8.5 Multiple (linear) regression showing factors independently associated with serum 25-OH D in patients

Predictor	Coefficient	SE Coefficient	*P*
Constant	76.87	30.95	0.023
Smoking, pack year history	-0.91	0.37	0.024*
Age, years	1.09	0.46	0.03*
PTH, pg/ml	-0.59	0.25	0.029*
PINP, ug/L	-0.31	0.26	0.246
OC, ug/L	1.51	1.40	0.298
CTX-1, ug/L	10.51	27.31	0.705
BMI, Kg/M^2	-1.59	1.26	0.223
Education Level, 1-3	-0.10	6.87	0.988
hs-CRP, mg/L	0.06	0.17	0.72
IL- 6, pg/ml	-0.36	0.86	0.678

*** Statistically significant**

Table 8.6 Multiple (linear) regression showing that no factors were independently associated with serum 25-OH D in controls

Predictor	Coefficient	SE Coefficient	*P*
Constant	19.28	48.03	0.69
Smoking, pack year history	-0.78	0.37	0.052
Age, years	-0.07	0.53	0.895
PTH, pg/ml	-0.31	0.33	0.364
PINP, ug/L	0.41	0.52	0.439
OC, ug/L	1.42	1.95	0.474
CTX-1, ug/L	25.55	51.5	0.626
BMI, Kg/M^2	-0.12	1.59	0.939
Education Level, 1-3	3.03	6.15	0.628
hs-CRP, mg/L	-1.77	2.96	0.557
IL- 6, pg/ml	3.79	2.55	0.154

8.3.8.2 Factors associated with osteopathy

Under univariate analysis, patients with osteopathy had higher serum P1NP, PTH and IL-6, and lower serum 25-OH D. Other factors did not reach statistical significance (Table 8.7). Under multivariable analysis (backwards, stepwise linear regression), serum 25-OH D was also independently predictive of *severity* of low BMD (lowest T-score at any area) in patients, as were age and BMI. Neither the BTMs nor the inflammatory markers were significant in this model (Table 8.8).

Table 8.7 Comparison of patients with normal BMD and those with osteopathy

	Normal BMD (n = 7)	**Osteopathy (n = 22)**	**CI**	***P***
	Mean (SD)	**Mean (SD)**		
P1NP, ug/L	45.2 (11.3)	66.2 (32.6)	4.24, 37.8	0.016*
OC, ug/L	12.99 (3.6)	13.91 (4.8)	-27.5, 4.6	NS
CTX-1, ug/L	0.436 (0.21)	0.489 (0.25)	-0.16, 0.26	NS
PTH, pg/ml	34.9 (11.4)	51.0 (20)	-28.74, -3.33	0.016*
25-OH D, nmol/L	46.6 (17.8)	34.0 (27.1)	-31.4, 6.3	NS
25-OH D tertiles#				
1st (<19.7 nmol/L)	*0*	*9*		
2nd (19.71 - 45 nmol/L)	*3*	*7*		0.041*
3rd (>45.1 nmol/L)	*4*	*6*		
Log IL-6, pg/ml	1.18 (0.22)	1.57 (0.69)	0.042, 0.737	0.03*
Log hsCRP, mg/L	0.6 (1.37)	1.35 (1.37)	-0.57, 2.07	NS
Age, years	40.3 (14.4)	45.5 (11.7)	-8.52, 19.04	NS
BMI, Kg/M^2	26.64 (5.5)	24.78 (4.97)	-7.16, 3.44	NS
Smoking, pack year history	11.2 (14)	18.7 (13.8)	-5.99, 20.99	NS

*Statistically significant, # presented as number (n)

Table 8.8 Multiple linear regression showing factors independently predictive of 'lowest T-score at any area'

	Coefficient	SE coefficient	*P*
Constant	-2.62	0.957	0.011
25-OH D	0.025	0.007	0.002
Age	-0.055	0.018	0.006
BMI	0.095	0.044	0.040

8.3.8.3 Factors associated with inflammation

Using ANOVA, hsCRP was analysed according to tertiles of 25-OH D. *Post-hoc* (Tukey) analysis showed that serum hsCRP levels were significantly higher in those in the lowest (*versus* highest) tertile of 25-OH D ($F = 3.44$, $P = 0.047$) (Figure 8.10). BMD (at the lumbar vertebrae L1:L4) were similarly divided into tertiles for ANOVA. Those with lowest BMD had the highest serum hsCRP levels ($F = 3.64$, $P = 0.04$) (Figure 8.11). As serum levels of IGF-1 were inversely correlated with hsCRP in preliminary analysis ($R = -0.435$, $P = 0.034$), ANOVA was also performed for tertiles of IGF-1. Figure 8.12 displays the statistically significant difference in serum hsCRP levels between tertiles of IGF-1 with *post-hoc* analysis (Tukey) showing that the first and third tertiles were significantly different, $F = 3.56$, $P = 0.046$.

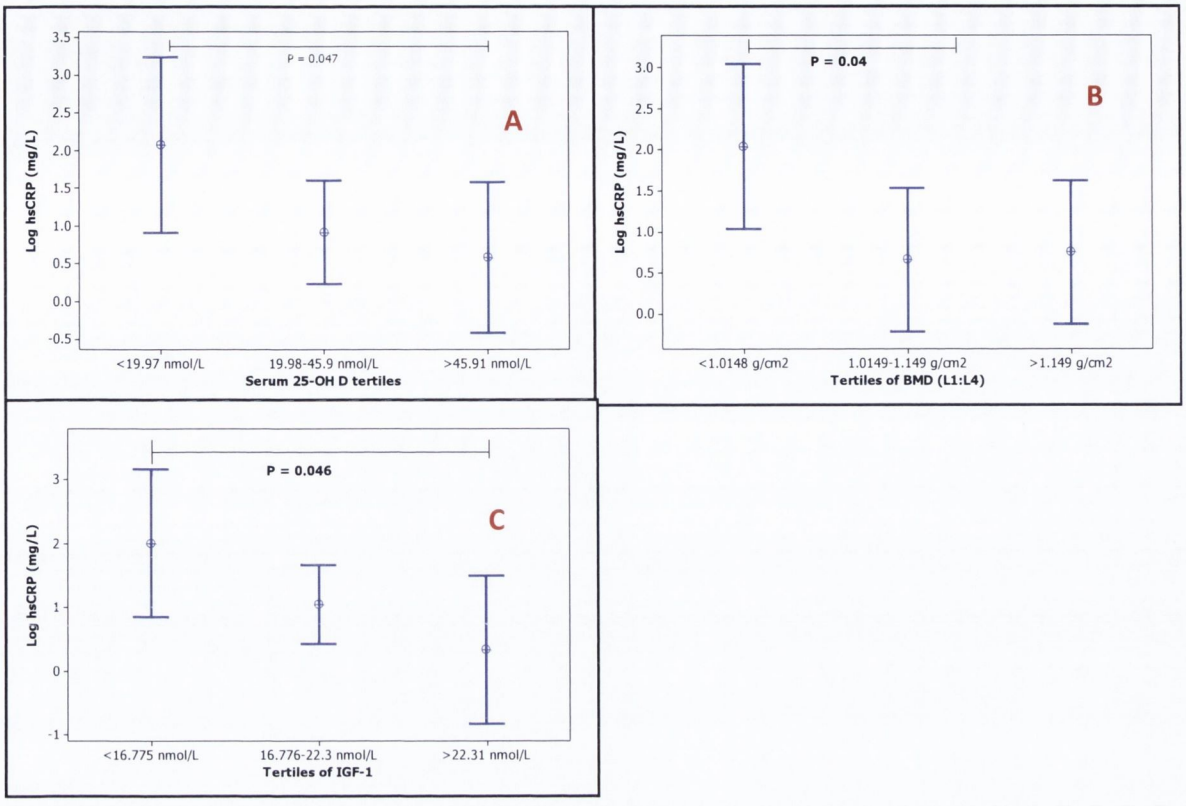


Figure 8.10 Interval plot showing serum (log transformed) hsCRP among patients by low, medium and high levels of serum 25-OH D (A)

Figure 8.11 Interval plot showing serum (log transformed) hsCRP among patients by tertiles of BMD (L1:L4) (B)

Figure 8.12 Interval plot showing serum (log transformed) hsCRP among patients by tertiles of IGF-1 (C)

8.4 Discussion

8.4.1 Summary of findings

This was a study examining BMD and the interplay between BTMs and inflammatory markers in chronic pancreatitis, involving 58 subjects (29 patients and 29 controls). Data from this study mirrors the earlier study described in Chapter 7: BMD was lower among patients with chronic pancreatitis at several bone sites, and the prevalence of osteoporosis was significantly higher than in matched, healthy controls who were matched for age, sex and education level. In the present study, data were presented which showed that biochemical

indices of bone turnover were abnormal in chronic pancreatitis. Both bone formation (P1NP, OC) and resorption (CTX-1) were raised in patients with chronic pancreatitis compared to controls. This therefore indicates that bone turnover is generally elevated in chronic pancreatitis, and the while the data are insufficient to show the minutiae of bone metabolism, it does appear that the coupling of formation to resorption is not entirely disrupted. There was evidence of higher systemic inflammation (hsCRP) in patients compared to controls. Factors known to affect BMD in other conditions (such as hypogonadism in IBD) appear not to play a role in the bone demineralisation process in chronic pancreatitis, and in fact, sex hormone levels were statistically similar between groups. Similarly, thyroid function did not differ statistically between groups indicating that hyperthyroidism-related bone loss does not account for the considerable differences in BMD among patients compared to controls. There appeared to be no age-effect, nor was there an association with BMI. It may be that the small sample size precluded finding an effect for sex among patients alone, as when the whole group were amalgamated, women had lower BMD. Female gender is a known risk factor for osteoporosis, particularly post-menopausally.

8.4.2 Abnormal BTMs

Only one other study previously investigated BTMs in chronic pancreatitis. In a study published in 2003, Mann *et al* examined BMD, serum 25-OH D and BTMS in 42 chronic pancreatitis patients and 20 controls. Bone formation markers OC and BAP were examined along with bone resorption marker CICP. Although differences were detected for BMD and serum 25-OH D across disease severity grades and compared to controls, no differences were detected for BTMs.[109] In fact, the present study is the first to show disrupted bone turnover in chronic pancreatitis compared to controls. Serum OC and P1NP were significantly higher among patients than among controls, showing that increased bone formation is a feature of the disease. While median levels of CTX-1 did not differ statistically, a quarter of patients had increased serum CTX-1 indicating increased bone resorption, which was statistically higher than the proportion of patients with raised levels (P = 0.016).. The bone formation marker P1NP may be of particular clinical significance, as this bone formation marker was independently predictive of osteopathy in patients. No controls had raised P1NP. Several

studies have examined BTMs in IBD. One Irish study by Gilman and colleagues investigated bone turnover in patients with Crohn's disease (CD) and ulcerative colitis (UC) compared to healthy controls.[276] Patients with CD and UC (measured in separate groups) had higher bone resorption (urinary NTX) than controls. However there were inconsistencies in the results, as BAP was higher in patients than in controls, while OC was lower, both being markers of bone formation. In an Italian study, Ardizzone *et al* investigated BMD and bone metabolism in IBD in 51 CD patients, 40 UC patients and 30 healthy controls.[277] OC and BAP were measured as bone formation markers and carboxy-terminal pyridinoline-cross-linked telopeptide of type 1 (ICTP) was measured as a marker of bone resorption. They reported that OC (but not BAP) was elevated in those with UC compared to controls, and ICTP was elevated in UC compared to both the CD group and controls. One study that investigated BTMs in relation to changes in BMD over time found that those with highest resorption (NTX) had the greatest reduction in BMD over 2 years.[278] In a Dutch study, Schoon *et al* found that bone turnover was reduced in patients with long-standing CD, although resorption (urinary) CTX and formation (BAP) was inversely related to BMD.[279] The partly inconsistent results for BTMs among IBD patients may be to a degree attributable to the many confounding factors related to the heterogeneity of IBD.[257, 280] The use of different markers in various studies, and the use of various methodologies may also account for the inconsistencies. For these reasons, serum P1NP has been recommended as the standard bone formation marker and serum/plasma CTX-1 as the standard bone resorption marker. In addition, while P1NP has relative stability, CTX shows significant diurnal variability and is affected by food intake, and therefore (as was done in the current study) samples should be drawn in the morning after an overnight fast.[280] The use of serum/plasma BTMs rather than urinary markers removes the additional potential for error in collecting and measuring urine and urinary creatinine, which is required for calculation. Studies investigating BTMs in chronic pancreatitis and IBD are summarised in Table 8.8.

Table 8.9 Summary of studies published since 2000 investigating BTMs in chronic pancreatitis and IBD

Author, year, Country	Study group (n)	Controls (n)	BTMs Formation/resorption	Findings
Duggan, Ireland (current study)	**Chronic pancreatitis (29)**	**Healthy, matched (29)**	**OC, P1NP/CTX-1**	**All BTMs higher in patients than controls** **Higher P1NP in patients with osteopathy**
Mann, Germany (2003)[109]	Chronic pancreatitis (42)	Healthy, matched (20)	OC, BAP/CICP	No differences in BTMs between patients and controls, despite lower BMD and vitamin D
Gilman, Ireland (2006)[276]	IBD (Crohn's disease, ulcerative colitis) (100)	Healthy, matched (100)	OC, BAP/-	BAP higher, but OC lower in patients *versus* controls
Duggan, Ireland (2004)[281]	CD, longstanding (44)	Healthy, matched (44)	-/uNTX	uNTX inversely correlated with vitamin K status (undercarboxylated OC)
Miheller, Hungary (2001)[282]	IBD (Crohn's disease, ulcerative colitis) (49)	Healthy (46)	OC/CTX-1	OC higher in CD compared to controls, but not in UC CTX-1 higher in both CD and UC compared to controls
Schoon, The Netherlands (2001)[279]	Longstanding Crohn's disease (26)	Healthy, matched (90)	OC, BAP/uCTX, deoxpyridoline	OC and BAP lower in patients than in controls BAP and uCTX inversely correlated with BMD
Ardizzone, Italy (2000)[277]	IBD (Crohn's disease, ulcerative colitis) (91)	Healthy, matched (30)	OC, BAP/uNTX	OC higher in patients than controls for UC only No difference in BAP
Dresner-Pollak, Israel, 2000[278]	IBD (Crohn's disease, ulcerative colitis) (36)		BAP, OC/NTX	Inverse correlation between NTX and rate of change of BMD Those in highest NTX quartile had biggest decrease in BMD over 2 years

8.4.3 Inflammation in chronic pancreatitis

Persistent, low-grade inflammation is a characteristic of chronic pancreatitis. However, much remains unknown about the mechanisms of inflammation in chronic compared to acute pancreatitis. Broadly speaking, inflammation plays a key role in tissue repair by eliminating injured cells. This process occurs *via* cytokine/chemokine-mediated action of neutrophils and macrophages. The chronic, low-grade inflammation promotes pancreatic fibrosis by facilitating activation of the stellate cells (which regulate synthesis and degradation of the extracellular matrix proteins that comprise fibrous tissue). Inflammatory mediators shown to be present in chronic pancreatitis include IL-6, IL-1β, TNF-α, and TGF-β.[283] One study reported that patients with pancreatic cancer had significantly higher IL-6 than those with chronic pancreatitis, who in turn had higher levels than normal controls. Szuster-Ciesielska *et al* also reported that patients with chronic pancreatitis had raised IL-6 (compared to healthy controls), although while serum TNF-α levels were elevated in patients with concomitant (alcoholic) liver cirrhosis and chronic pancreatitis, levels were not raised in those with chronic pancreatitis alone. Inflammatory markers may be affected by toxins or by clinical features of disease such as DM. Sliwinska-Mossón and colleagues demonstrated that IL-6 levels in the sera of smoking chronic pancreatitis patients were >7 times greater than in non-smoking patients. Hansen *et al* showed a more than three-fold increase in the IL-6 levels of chronic pancreatitis patients with DM compared to those with normal glucose tolerance. In the current study, the assay used for the measurement of IL-6 was insufficiently sensitive to detect levels <3 pg/ml. More than a third of patients had levels above this reference compared to only 13.8% of healthy controls; however this did not reach significance. Nevertheless, data from the present study showed higher hsCRP in patients *versus* controls (Table 8.10). Median levels for patients (3.15 mg/L) were however lower than described for a Polish study (7.7 mg/L) of 45 chronic pancreatitis patients.[284] For controls, levels in the present study (0.9 mg/L) were largely comparable to the literature, including studies from Korea (0.6-0.9 mg/L[285], 0.7-1.0 mg/L[263]), and Italy (1.4 mg/L)[260], but lower than levels from the aforementioned Polish study (5.0 mg/L)[284]. Levels were higher than in a Japanese study (0.25 mg/L)[286]; inflammatory markers in the Japanese population are known to be lower than in Caucasian populations.[262]

Table 8.10 Levels of serum hsCRP for healthy subjects, chronic pancreatitis, and pancreatic cancer: a comparison between the current study and the literature

Author, country (year)	n, sex	Type	Age	Median (Q1-Q3)
Duggan, Ireland (current study)	**29, mixed**	**Healthy, community-dwelling**	**Middle-aged**	**0.9 (0.5-2.15)**
Nakamura, Japan (2011)	751, women	Healthy, community-dwelling	Elderly	Low: <0.25 Medium: 0.25-0.59 High: >0.59
Miyake, Japan (2010)	25, mixed	Healthy	Middle-aged	0.25
Mroczko, Poland 2010)	70, mixed	Healthy	Middle-aged	5.0
Kim, Korea (2007)	39, women	Attendees at osteoporosis clinic	Pre-menopausal	0.6 (0.4-1.2)
			Post menopausal	0.9 (0.6-1.6)
Schett, Italy (2006)	906, mixed	Healthy, community-dwelling	Middle-aged	1.4 (0.8-3.0)
Koh, Korea (2005)	4,693, women	Attendees at health promotion centre	Pre-menopausal, >30 years	0.7
			Post-menopausal	1.0
Duggan, Ireland (current study)	**29, mixed**	**Chronic pancreatitis**	**Middle-aged**	**3.15 (1.3-7.75)**
Mroczko, Poland (2010)	45, mixed	Chronic pancreatitis	Middle aged	7.7
Miyake, Japan (2010)	17, mixed	Pancreatic cancer	Middle-aged	2.53
Mroczko, Poland (2010)	78, mixed	Pancreatic cancer	Middle-aged	17.7

8.4.4 Raised hsCRP and metabolic bone disease

To date, no prior studies have examined the link between hsCRP and bone metabolism in chronic pancreatitis, nor has this association been explored in IBD. Among healthy subjects, a link between hsCRP levels and bone metabolism has been described by several studies. In a prospective population-based survey[260], 906 Italian men and women were analysed every five years and data on fractures and serum hsCRP were recorded. They reported that the highest incidence of non-traumatic fractures occurred among those in the highest hsCRP tertile. Moreover, hsCRP was associated with reduced bone formation (OC) and serum 25-OH D deficiency. However, hsCRP did not directly correlate with radiological BMD measures. In a study of 150 post-menopausal and 39 premenopausal women, Kim *et al* found that BTMs were altered in those with osteoporosis (bone formation was reduced and resorption was increased). Additionally, there was a direct correlation between BTMs and systemic inflammation, measured by hsCRP. In a further cohort study of 751 community-dwelling elderly Japanese women, there was an increased risk (hazard ratio 2.4) of fracture in those with the highest hsCRP (>0.59 mg/L) compared to the lowest levels (0.25 mg/L).[262] Therefore, in systemic inflammatory conditions such as chronic pancreatitis with persistently elevated hsCRP, it is reasonable to assume that the high prevalence of osteoporosis may be at least partly linked to this.

8.4.5 The role of vitamin D

The optimal serum level of 25-OH D remains controversial. Some recommend <75 nmol/L as the optimal cut-off[198], while others suggest that <50 nmol/L is a more realistic and attainable goal.[287] In its most severe form, deficiency of 25-OD D leads to osteomalacia (failure to mineralise newly formed osteoid), equivalent to childhood rickets (see Chapter 7). Prolonged serum levels of <25 nmol/L (vitamin D 'deficiency') are thought to be required for the development of osteomalacia, while levels between 25 nmol/L and 75 nmol/L are considered to be vitamin D 'insufficiency', resulting in osteoporosis[198]. In the current study, 2 in 5 patients had levels below the 'osteomalacia' cut-off (<25 nmol/L), while no controls were similarly deficient. Despite this, no patients had a diagnosis of osteomalacia, although as discussed in Chapter 7, these bone diseases are indistinguishable on DXA, and symptoms of

osteomalacia tend to be vague and unspecific (bone pain, muscle weakness). Despite the difference in 'deficiency' levels (<25 nmol/L), there was no difference in the proportion of patients and controls with 25-OH D levels below 50 nmol/L. In an Irish IBD group, Gillman *et al* found that patients with CD and UC had lower serum 25-OH D than controls.[276] However serum 25-OH D in both disease groups was notably high – higher than for both the patient and control group in the present study. Mean (SD) levels were 71.6 (33) nmol/L for CD and 63.9 (20.5) nmol/L for UC. In the current study, mean levels for patients were 37 (25.4) nmol/L, and for controls were 50.8 (23.5) nmol/L. The difference in vitamin D levels in the two studies cannot be explained by geographical differences, as both studies recruited patients and controls from an Irish population, and both throughout the calendar year. The Gilman study excluded those on supplements, which was also an exclusion criterion for the present study. Patients with chronic pancreatitis had marginally higher BMI than the CD group (25.2 (5.2) Kg/M^2) *versus* 24.3 (5.2) Kg/M^2) and controls in the present study had an even higher BMI (27.3 (3.7) Kg/M^2). As vitamin D may be sequestered in adipose tissue, higher BMI is associated with reduced bioavailability of vitamin D.[233] However, the disparity in serum 25-OH D is unlikely to be due to such relatively modest BMI differences. The difference might be attributable to lifestyle variations, as only 13.7% of the patients and controls in the current study finished 2^{nd} level education. However, this is conjecture as neither education level nor socio-economic status was reported in the IBD study. Smoking was also considerably higher in the present study than in the IBD study. Almost 7 in 10 chronic pancreatitis patients were current smokers, much higher than reported in the IBD study (25% of CD patients and 19% of UC patients). The relationship between smoking and bone metabolism is discussed later.

8.4.5.1 Vitamin D and inflammation

It is certain that vitamin D is crucial for good bone health, having the primary function of facilitating optimal intestinal absorption of dietary calcium. In a chronic malabsorptive condition such as chronic pancreatitis, the mechanisms for the development of vitamin D deficiency are clear: malabsorption, poor diet, poor physical activity, and lack of sunlight are all likely to play a part. However a key vitamin D-related effect on bone integrity in chronic

pancreatitis has not previously been considered in studies. It is feasible that vitamin D acts as an anti-inflammatory agent suppressing chronic inflammation.[257] In a review, Raftery *et al*[288] described the potential immune-modulating role of vitamin D in IBD. While much of the evidence to date is from *in vitro* or animal studies, the authors described a study in a mouse model[289] in which vitamin D and calcium supplementation prevented IBD symptoms. In another study, Kelly *et al* reported that IL-10 (an *anti*-inflammatory cytokine) was significantly lower in IBD patients who were vitamin D deficient compared to those who were vitamin D replete.[290] The role of vitamin D in bone metabolism, which is interlinked with that of PTH, is complex and incompletely understood. While vitamin D may positively affect bone by enhancing osteoblast differentiation and effecting bone matrix synthesis, paradoxically, high levels of the active vitamin D metabolite 1,25-OD D may be a risk factor for the development of osteoporosis in IBD.[257] Neither the clinical nor the biochemical effects of vitamin D supplementation on bone metabolism in chronic pancreatitis have been investigated. Studies investigating the potential effects of vitamin D on bone metabolism and inflammation would be of considerable interest.

8.4.6 The effect of smoking

Current smoking was particularly high among patients in this study (69%), higher than among controls (17.2%), and higher than the reported average level in Ireland for 2011/12, according to the National Office for Tobacco Control (22%)[291]. Smoking was still considerably high even when social status was taken into consideration. While most of the patients in this study had finished 1st level education or less, this proportion was not different from the control group. Those in the lowest income categories of the National survey had marginally higher smoking tendency (25.4-27.2%)[291], but still far below the levels among subjects in this study. Smoking appeared to be related to vitamin D status; those with low vitamin D (<50 nmol/L) were the heaviest smokers and multivariable analysis showed that smoking was an independent predictor of vitamin D status. Smoking may exert an independent effect on vitamin D status by hypothetically altering the hepatic metabolism of vitamin D by influencing 25 hydroxylase in the liver and lowering serum 25-OH D,[292] and studies in other groups have mirrored the inverse vitamin D/smoking relationship seen in the current

study.[293-294] Although there was no relationship between smoking and BMD in this study, the prior study described in Chapter 7 showed that those in the highest smoking tertile had the lowest BMD. Other studies have demonstrated a negative effect of smoking on BMD by altering GI calcium absorption[293], reducing oestrogen levels[292], and by a direct effect of nicotine on osteoblastic bone formation.[292]

8.4.7 The role of sex hormones, thyroid function and IGF-1

There was no evidence of hypogonadism in patients with chronic pancreatitis in this study, and therefore this is an important distinction to make between chronic pancreatitis- and IBD-related osteoporosis. Similarly, there was no suggestion of a hyperthyroidism-related effect on BMD. While the data do not support IGF-1 as a unique driver of osteoporosis in chronic pancreatitis (levels were not different compared to controls), hsCRP levels were highest in the lowest tertile of IGF-1, indicating that IGF-1 levels may be associated with a systemic inflammatory state. Nevertheless, while IGF-1 has been suggested as an early serum marker for osteoporosis[274, 295], data from the current study did not support an association between IGF-1 and BMD.

8.4.8 Aetiology of osteoporosis in chronic pancreatitis

The aetiology of osteopathy in chronic pancreatitis remains elusive, but is likely to comprise a complex array of inter-related factors. Despite modest sample size in the present study, there were certain patterns apparent in the data which may help to characterise the nature of osteoporosis for this condition. Firstly, the data showed that as well as low BMD, there was an increased bone turnover in patients with chronic pancreatitis. Secondly, the data showed that sensitive markers of systemic inflammation were higher in chronic pancreatitis patients than in controls. Furthermore, there was a direct statistical association between BMD and sensitive serum inflammatory markers (hsCRP and IL-6). This suggests that the bone destruction process in chronic pancreatitis is at least partly inflammatory in nature. This pivotal finding has not previously been demonstrated in patients with chronic pancreatitis. Thirdly, serum 25-OH D deficiency also appears to have a central role and was similarly

associated with lower BMD. These factors may be related, as vitamin D is known to have anti-inflammatory properties. Lastly, serum 25-OH D deficiency was also associated with heavier smoking, which itself poses an independent threat to bone integrity. Table 8.10 lists the factors that are likely to contribute to the high prevalence of osteopathy in chronic pancreatitis, and are divided into those factors which are modifiable and those which are non-modifiable. Factors with potential for modification through direct nutritional intervention are highlighted. Figure 8.10 illustrates the suggested interplay between pro-inflammatory cytokines, smoking and vitamin D (deficiency), with the resultant induction of a pro-resorptive state in chronic pancreatitis.

Table 8.11 Modifiable and non-modifiable risk factors for osteopenia and osteoporosis in chronic pancreatitis

Modifiable risk factors	Non-modifiable risk factors
Malnutrition[#] Low BMI Low muscle mass / sarcopenia	Increasing age Female gender
Malabsorption[#] Especially untreated or poorly managed	Previous low-trauma fracture Family history of osteoporosis
Poor diet[#] Vitamin D, calcium intake, and overall quality and quantity	
Low serum 25-OH D levels[#]	
Smoking	
Poor mobility / reduced physical activity	
Chronic inflammatory state (potentially modifiable)	

Potential for nutritional intervention

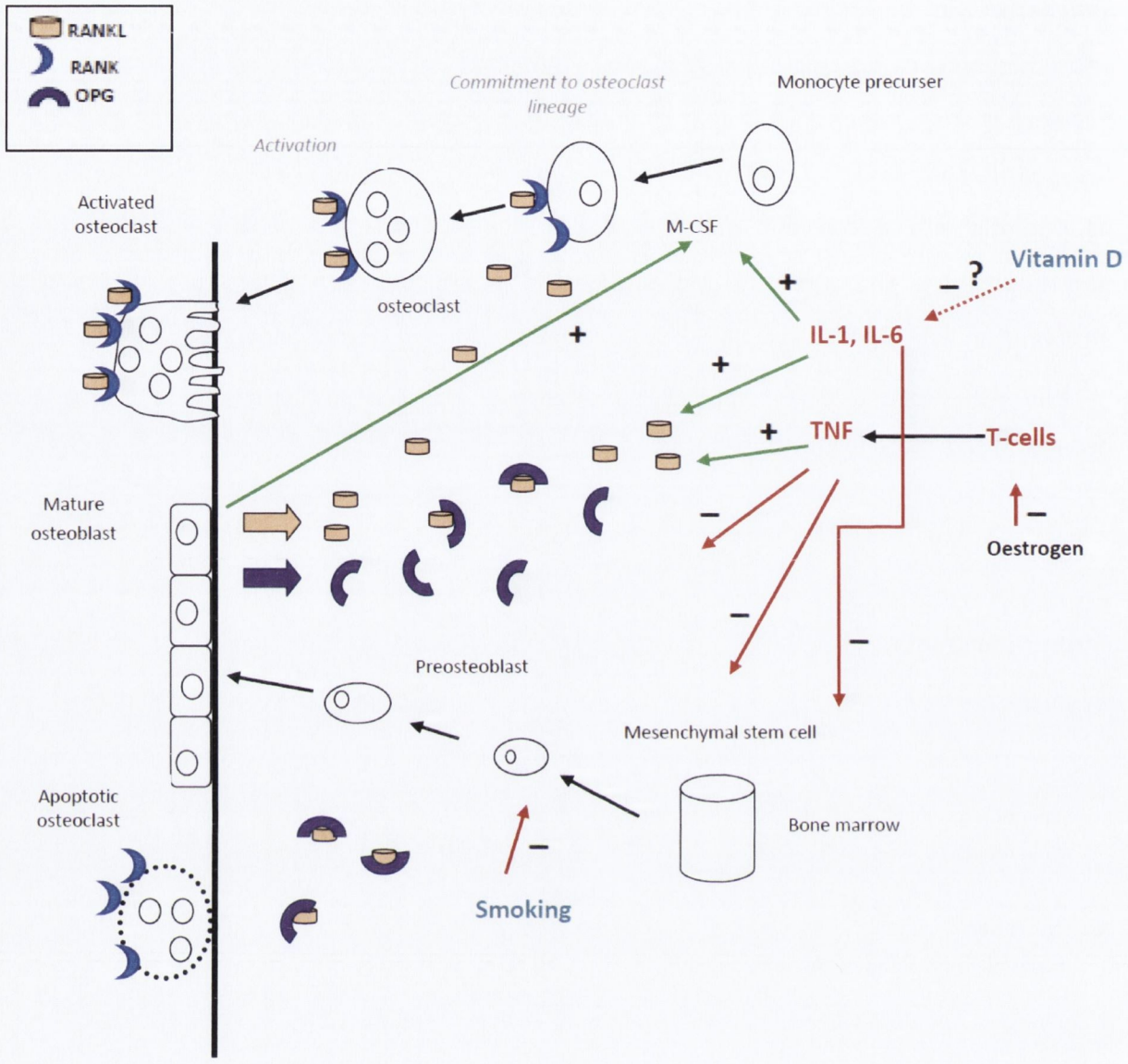


Figure 8.10 The suggested role of proinflammatory cytokines, smoking and vitamin D (deficiency) in promoting a resorptive state in chronic pancreatitis

Proinflammatory cytokines IL-1, IL-6, along with TNF, enhance the production of RANK, suppress the production of OPG, and suppress osteoblastic differentiation. A vitamin D – deficient state results in heightened inflammation. Smoking negatively affects osteoblastic development and reduces oestrogen.

8.4.9 Study limitations

Sample size was the main limitation of this work, and although differences were detectable broadly between groups, more in-depth subgroup analysis was likely to be underpowered to detect differences if they existed. In addition, exocrine dysfunction was not formally measured, and therefore, the effect of PEI on BTMs was not measured. To detect higher IL-6 and TNFα values, a decision was made to use the standard assays rather than the high sensitivity assays. For IL-6, the effect was milder, as many subjects had detectable values. However, for TNFα, failure to use the high sensitivity assay meant that results from that assay were unusable.

8.4.10. Study strengths

As one of only two studies to have investigated BTMs in chronic pancreatitis, this study provides original and novel data on BTMs in chronic pancreatitis. Rigorous methodology was applied, so the potential pitfalls of BTM measurement were minimised and the data was reasonably consistent.

8.4.11 Conclusions

These data showed that bone turnover (both formation and resorption) were elevated in patients with chronic pancreatitis compared to controls. This may account for the significantly higher prevalence of osteoporosis which was described in this study and in the previous cohort study in Chapter 7. Moreover, a relationship between systemic inflammation and BMD was demonstrated, showing for the first time that the bone demineralisation seen in chronic pancreatitis may be in part driven by chronic systemic inflammation. In addition, a deficiency in serum vitamin D was also shown to be a related factor, as was a considerably high smoking status among patients. Together these factors provide an avenue for potential modification of risk factors which may reduce bone loss in chronic pancreatitis, prevent osteoporosis and ultimately avert fractures.

Chapter 9 Discussion

9.1 Summary of objectives and findings

The dual-objectives of this thesis were to examine nutritional practice in acute pancreatitis, and nutritional status in chronic pancreatitis. To achieve these objectives, 7 inter-related studies were conducted, the first 3 of which concerned acute pancreatitis. The findings from these studies are summarised as the following:

1. Blind, bedside NJ tube insertion was a practicable, safe and cheaper alternative to endoscopic tube insertion, thus facilitating the timely implementation of EN in patients with acute pancreatitis.

2. Both shortcomings and strengths in the local clinical management of acute pancreatitis were identified in this institution compared to best practice as laid out by international guidelines. Strengths included low mortality, high use of EN *versus* PN for feeding, and a reduction in delays in starting feeding over the study period. Shortcomings included an overall late start in implementing feeding (mean 4.1 days), and deficiencies in data collection.

3. Shortcomings in the nutritional management of acute pancreatitis were demonstrated by an international survey, including a continued reliance on PN, and poor adherence to / awareness of practice guidelines.

To examine nutritional status in chronic pancreatitis, a cohort study recruited 131 subjects (62 chronic pancreatitis patients and 66 controls) which provided data on malnutrition and bone health. This was followed by a systematic review and meta-analysis of the prevalence of osteopathy in chronic pancreatitis. Finally, a second cohort study recruited 58 subjects (29 chronic pancreatitis patients and 29 controls) in whom BTMs, systemic inflammation and BMD was measured. The findings of these studies are summarised as follows:

1. Nutrient deficiencies (of vitamins A and E, and especially D) were common; however vitamin toxicity also occurred. An obese-sarcopenic state (characterised by depleted muscle mass in the presence of obesity) appeared to be common for chronic pancreatitis patients. Under treatment with PERT was also a feature, while type 3 DM, malabsorption and pain were frequently reported. Patients were notably heavy smokers, and many continued to abuse alcohol.

2. Osteoporosis and osteopenia appeared to be major clinical concerns for patients with chronic pancreatitis. A third of Irish patients had osteoporosis, which was higher than the international pooled prevalence of 23.4%. Although the data were clinically and statistically heterogeneous, it did appear that heavy smoking and malabsorption were associated with a greater risk of low BMD.

3. There was higher bone turnover in patients with chronic pancreatitis than in controls, as measured by biochemical indices of bone metabolism, as well as higher systemic inflammation according to sensitive inflammatory markers. While the mechanisms of bone demineralisation have not been elucidated in chronic pancreatitis, there appears to be a link between inflammation, low serum 25-OH D levels, heavy cigarette smoking, and osteoporosis which warrants closer scrutiny in future studies.

9.2 Novel and original contributions to knowledge

9.2.1 Acute pancreatitis

These studies on acute pancreatitis represented the first report of bedside NJ tube insertion in Ireland, and among the first in the UK signifying an innovative, cost-effective expansion of the dietetic role. The dietitian survey which assessed international practice was the largest and most extensive such study conducted to date, and was the first to compare practice in different countries / continents. For the first time, deficiencies in practice *versus* the guidelines were highlighted providing a valuable opportunity for intervention.

9.2.2 Chronic pancreatitis

For chronic pancreatitis, up to date data were obtained for malnutrition and nutrient deficiency, specifically in an Irish and Western European setting. Many of the oft-cited studies were published more than 20 years ago, and many were conducted on different populations (for example Asian or African patient groups). The finding of hypervitaminosis in particular has not previously been documented, and together, these data provide a framework for updated clinical guidelines on this topic. Results from the prevalence of osteoporosis in the first cohort study were notably high, higher than what was expected at the outset. This was the first analysis of osteoporosis in an Irish patient group, and among the first in Europe. In fact, the first ever meta-analysis of the data showed that prevalence in the Irish group was higher than the average pooled prevalence from 11 published studies. This led to the first comprehensive investigation to date of bone metabolism in chronic pancreatitis. By identifying statistical associations between osteopathy and systemic inflammation, as well as smoking and vitamin D, these data provide a novel insight into the complex process of bone demineralisation in chronic pancreatitis.

9.3 Implications for clinical practice

9.3.1 Acute pancreatitis

Results from the NJ insertion study highlighted the resource savings that are possible by implementing such a process, as well as highlighting the potential for extension of the role of members of the medical team. This procedure remains the first-line insertion method in this institution thereby conferring ongoing cost-savings and removing considerable barriers to early implementation of EN. The success of this process is reflected in the notably high use of EN rather than PN indentified in the 3-year acute pancreatitis audit study (Part 2). However, other findings identified deficits in practice and thus emphasised the need to continue to strive for evidence-based practice. Furthermore, results from the international acute pancreatitis practice survey underlined general deficits in the nutritional management of acute pancreatitis, including a continued reliance on PN. Although the aim to feed early appears widespread, perceived barriers to EN include medial preference. Therefore both

large-scale and local education is necessary to ensure that all clinicians are at least aware of the relevant guidelines. For institutions that receive tertiary referrals, and where management protocols do not exist, their development should be encouraged. Evidence-based feeding protocols, where lacking, could be initiated and developed by the pancreatic dietitian in collaboration with the medical or surgical team. As practice in university hospitals was more consistent with the guidelines, education targeting smaller district hospitals may help to improve and support the implementation of best-practice.

9.3.2 Chronic pancreatitis: malnutrition

Data arising from the chronic pancreatitis malnutrition study had clear benefits to patient care and clinical practice. The results provided insight into type 3 DM, exocrine function, PERT use, symptoms, supplement use, and vitamin deficiency, all of which will ameliorate the clinical consult. The data allowed for the development of several useful clinical tools having the potential to affect change in practice. Figure 9.1 provides an evidence-based algorithm for administration of PERT in chronic pancreatitis. This figure is based on prior work by several authors[211-213] as well as details from this thesis. In Chapter 6, Table 6.13 summarised the principles of nutritional assessment and strategies for management for patients with chronic pancreatitis-related type 3 DM. This table represents the first set of suggested nutrition/lifestyle-related strategies to deal with this difficult condition. Figure 9.2 illustrates a comprehensive flowchart for the nutritional assessment and management of patients with chronic pancreatitis. This figure includes the most recently-published evidence and incorporates data published from the current studies. Crucially, this flowchart incorporates the management of PERT, bone health and type 3 DM, as well as malnutrition, nutrient deficiency, social issues, and dietary management highlighted by this work which provides an invaluable framework for the management of this nutritionally-complex patient group.

9.3.3 Chronic pancreatitis: bone health studies

Data from the fist cohort study described in Chapter 7 was strengthened by data from the second cohort study (Chapter 8), as well as the systematic review (Chapter 7): patients with chronic pancreatitis were at a higher risk of developing osteoporosis than healthy controls.

Smoking, vitamin D and a pro-inflammatory state appeared to be associated with lower BMD among patients. Clinically, this underlines the importance of strong medical advice regarding smoking cessation for patients with chronic pancreatitis. Dietary intervention should focus on ensuring adequate dietary calcium and vitamin D, with supplementation where appropriate and regular follow-up to ensure repletion of serum 25-OH D levels. The AGA, as part of its recommendations on osteoporosis in GI disease recommended that patients with one or more known osteoporosis risk factors should undergo initial screening with DXA[222]. These recommendations were for IBD, coeliac disease and post-gastrectomy patients and did not include chronic pancreatitis. The AGA stated that while 'the path of least resistance' would be to perform a DXA on all patients with GI disorders that this would result in numerous unnecessary tests. On the other hand, those with normal BMD might be 'lulled into a false sense of security' where concomitant risk factors might increase the true risk of osteoporosis despite a normal DXA result[222]. Therefore, the AGA recommended that those who have experienced a vertebral fracture, are post-menopausal, on corticosteroid therapy (in IBD) should be tested, but 'common sense' on the part of clinicians was also recommended. Those with at least one risk factor should probably undergo initial screening with DXA.[222] While the AGA did not include chronic pancreatitis in the guidelines, data from Chapters 7 and 8 supports its inclusion in future document revisions. Suggested management strategies for bone health in chronic pancreatitis developed as a consequence of these studies (adapted from the AGA guidelines) are provided in Figure 9.3. These were further supported by Table 8.10 (Chapter 8) which identified risk factors for the development of osteoporosis in chronic pancreatitis.

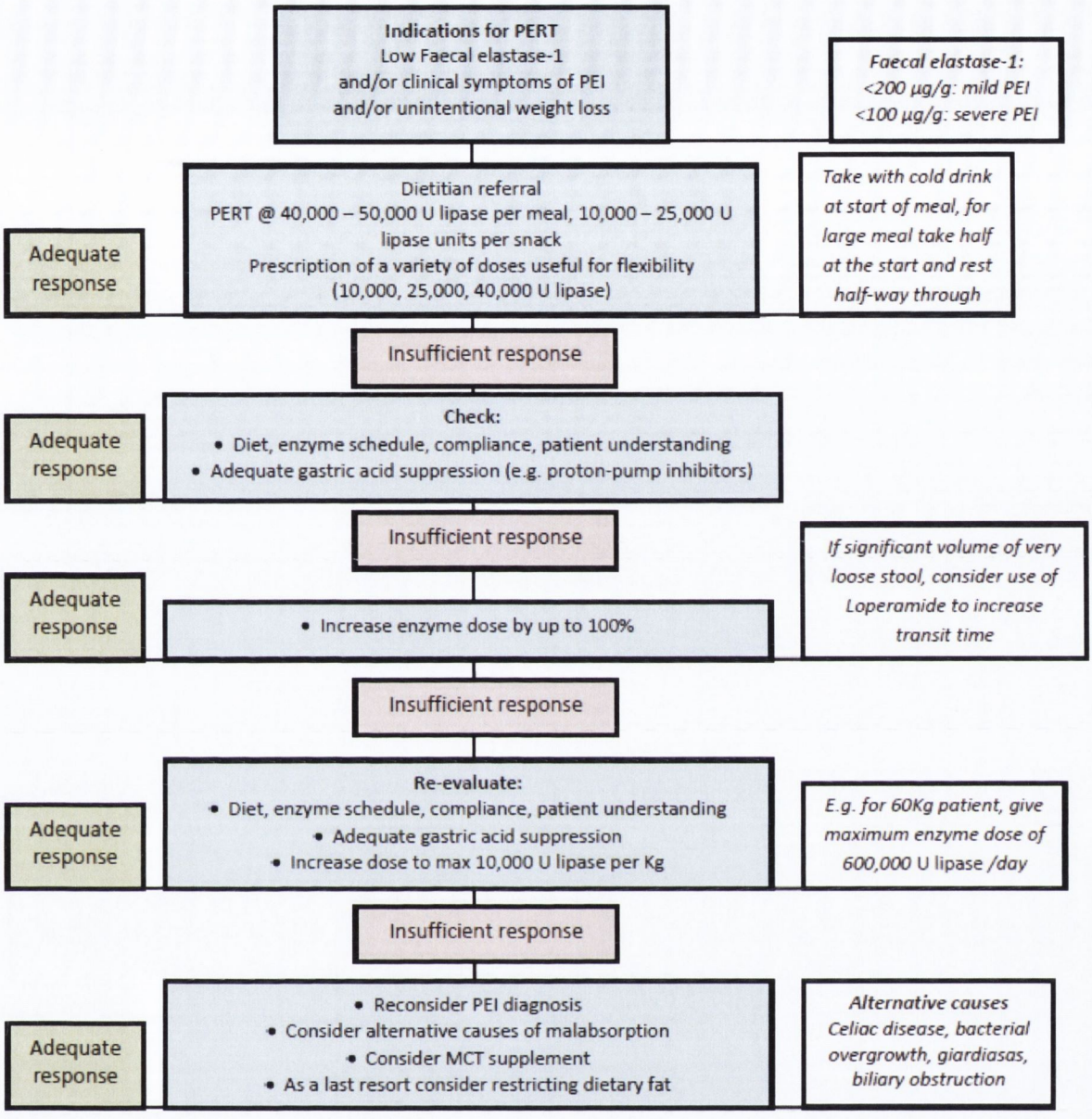


Figure 9.1 Suggested algorithm for PERT in chronic pancreatitis

Based on Dominguez-Munoz (2007)[211], Layer & Keller (2003)[213] & Imrie (2010)[212]

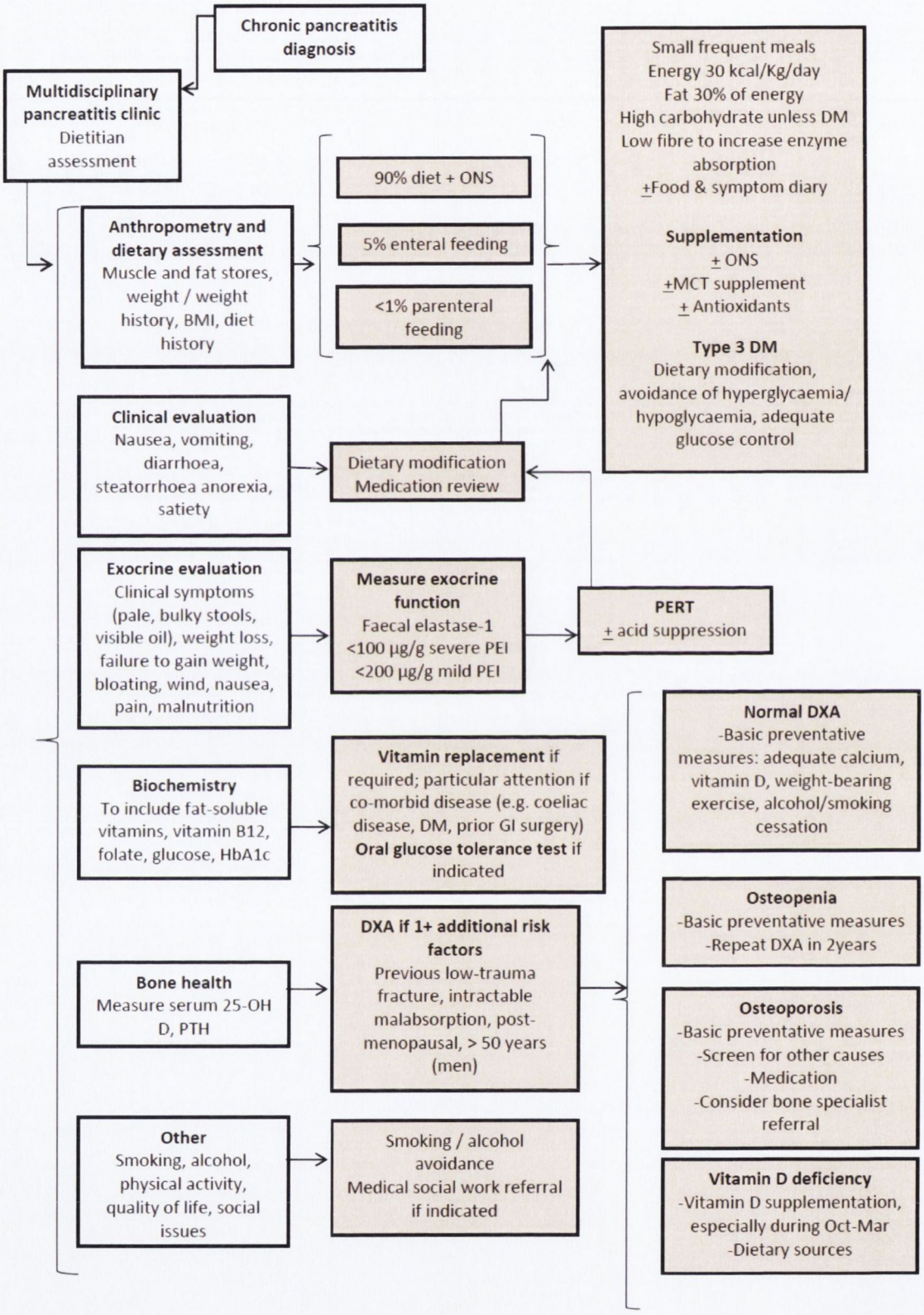


Figure 9.2 Evidence-based algorithm for the nutritional management of patients with chronic pancreatitis

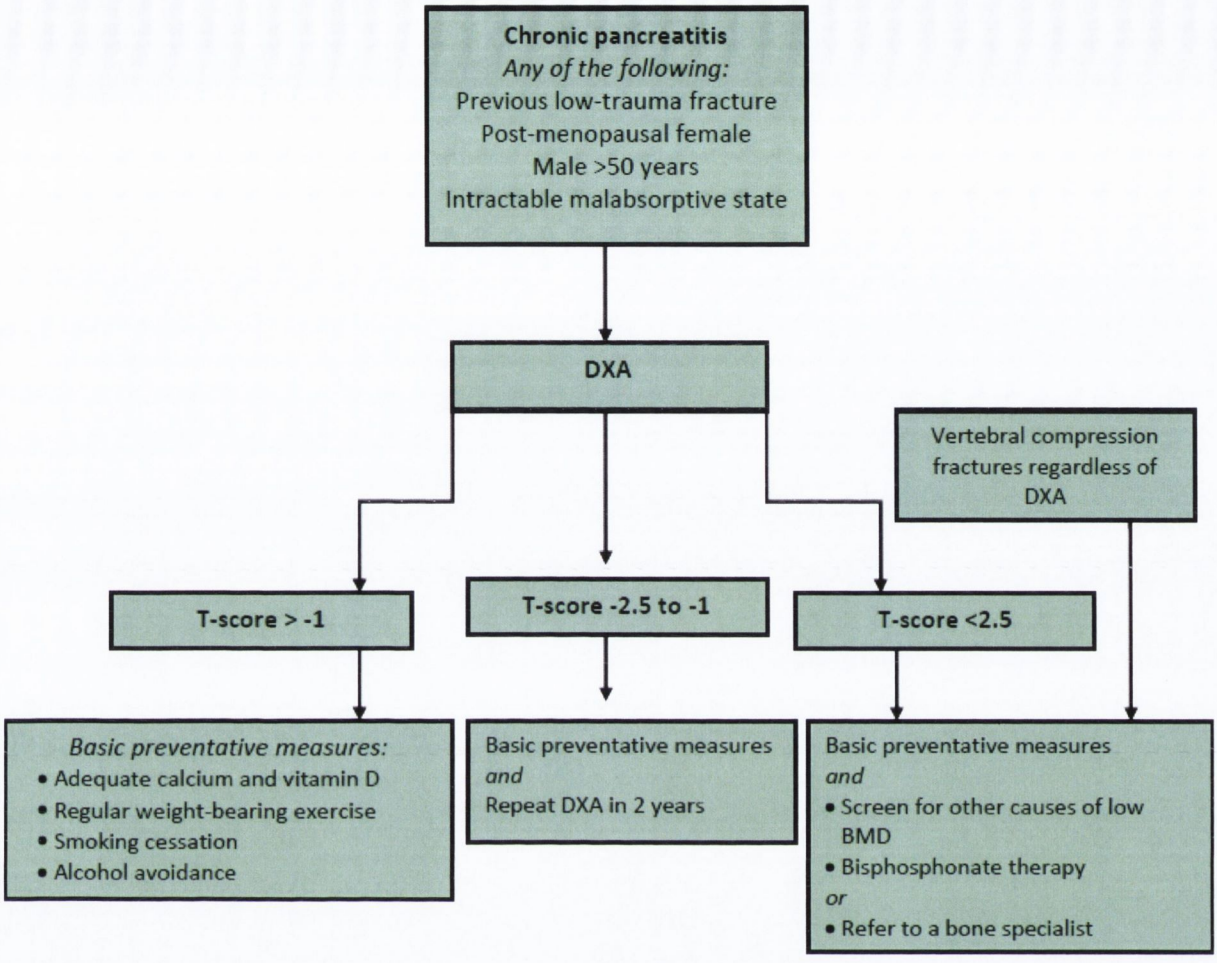


Figure 9.3 Suggested management of bone health in chronic pancreatitis based on the AGA management approach for osteoporosis in gastrointestinal disorders [222]

9.4 Publication of suggested practice-based guidelines from this thesis

Results from Chapter 5 on the adherence to guidelines in acute pancreatitis highlighted the fact that the publication of practice guidelines is no guarantee of implementation. Problems with nutritional management in *acute* pancreatitis are likely to be mirrored for *chronic* pancreatitis; including a lack of specialised dietetic care, poor awareness / dissemination of guidelines, and suboptimal support from some medics regarding nutrition. Well-though out education strategies for dissemination and promotion of guidelines are vital. This may include presentation at local and international meetings, as well as inclusion of pertinent studies and reviews in international consensus guidelines. In addition, the development of visual aids such as flow-diagrams should help with the adoption of guidelines. Of the 5 practice-based suggested guidelines developed from these studies, 3 have been published to date (Table 9.1).

To follow-on from the studies, there are several key points which are necessary to improve pancreatitis care in Ireland and internationally:

1.) An improvement is required regarding adherence to existing guidelines for acute pancreatitis. This should be done by mandating routine audit of services, both clinical and nutritional. The UK acute pancreatitis guidelines[26] recommend that all patients are included in prospective audits to encourage improved standards of care, but there are no mandated guidelines, and none specific to Ireland. Mandatory audits would serve to address this gap. In addition, education around the existing guidelines through publication, conferences and professional bodies would increase awareness, both locally and nationally.

2.) For chronic pancreatitis, in the absence of existing guidelines, peer-reviewed publication of the results of these studies and others is central to disseminating findings. Therefore, timely and high-impact publication of the work within this thesis was a priority from the onset. In addition to the publication of original data, the author prioritised the publication of review articles, both peer-reviewed and non-peer-reviewed, which included clinically-relevant algorithms and tables as described above (Table 9.1). This had the intention of

encouraging a more evidence-based, standardised approach to the nutritional management of chronic pancreatitis. In addition, presentation at local and international meetings was done to inform the pancreatic community of these findings (Appendix B). The author also became highly involved in the Pancreatic Society of Great Britain and Ireland, including the establishment of a nutrition interest group (current membership >50 dietitians) within this society. The author was furthermore invited to join the council of this society as a nutrition-representative. This facilitated the promotion of a nutrition-focused agenda. Through this work, the author was also invited to join a guidelines committee of the Pancreatic Society / National Institute of Clinical Excellence (UK) which is responsible for developing or updating pancreas-specific clinical guidelines over the next few years. These steps were considered a vital follow-up of the clinical studies which comprise this thesis.

Table 9.1 Guidelines produced from this thesis

Suggested management guidelines	Figure	Pertaining to chapter
Algorithm for PERT in chronic pancreatitis[296]	9.1	6
Algorithm for the Nutritional Management of Chronis Pancreatitis[296-297]	9.2	6
Suggested principles of nutritional management and management strategies for type 3 diabetes in chronic pancreatitis[296]	6.13	6
Modifiable and non-modifiable risk factors for osteoporosis and osteopenia in chronic pancreatitis (Table)	8.11	7/8
Suggested management of bone health in chronic pancreatitis (based on the AGA management approach for osteoporosis in GI disorders)	9.3	7/8

9.5 Suggestions for future research

9.5.1 Acute pancreatitis

While the nutritional management of patients with acute pancreatitis has evolved and developed over the last 10-15 years, there are several key areas which require large scale, well-designed, controlled trials to establish best practice. The available guidelines are deficient in several areas of clinical importance due to lack of research in those areas. Specifically, the following areas of nutrition support require further research:

1. The effect of timing of EN on outcomes
2. A comparison of NG *versus* NJ feeding in severe acute pancreatitis
3. An investigation of the most appropriate mode of feeding for patients with mild acute pancreatitis

Other areas requiring research include: the provision of PERT with EN; the use of enteral glutamine; and the use of probiotics in acute pancreatitis. Furthermore, an investigation of pancreatic function following severe acute pancreatitis is warranted, particularly around the areas of exocrine function and endocrine changes leading to type 3c DM.

9.5.2 Chronic pancreatitis: malnutrition

Upon completion of this study, there were several identifiable gaps in the literature which would benefit from further investigation:

1. A formal systematic review of the literature on the prevalence of nutrient deficiencies in chronic pancreatitis
2. An investigation of the impact of PERT on fat soluble vitamin levels
3. Large-scale studies investigating the relationship between clinical and subclinical nutrient deficiencies in chronic pancreatitis

4. Characterisation of type 3c DM in chronic pancreatitis; specifically examining levels of insulin, glucagon, pancreatic poly-peptide, C-peptide, oral glucose tolerance and HbA_{1c}
5. A study investigating QOL in Irish chronic pancreatitis patients
6. Analysis of dietary intake
7. CT-based analysis of body composition and sarcopenia

9.5.3 Chronic pancreatitis: bone health

While the data from individual studies strongly suggest a high prevalence of osteoporosis in chronic pancreatitis, there are notable gaps in the literature which represents key opportunities for research.

1. Further well-designed, prospective prevalence studies are warranted to provide additional evidence for the prevalence of osteoporosis in chronic pancreatitis. In particular, such studies should be adequately powered to detect *a priori* differences within subgroups, and should have a well-matched control arm.
2. Data on the prevalence of low-trauma fractures in chronic pancreatitis are required, as fractures are the most important clinical outcomes for osteoporosis and represent considerable morbidity and economic concern.
3. Further investigation of the mechanisms which drive bone demineralisation
4. Further investigation of the effect of chronic systemic inflammation and the potential immuno-modulatory effects of vitamin D

9.5.4 Future directions

The work described herein has led to the establishment of an active pancreatic/nutrition research core between The Trinity Centre for Health Sciences at Tallaght Hospital, The Centre for Pancreatico-Biliary Diseases at Tallaght Hospital, and The Hepato-Biliary Surgical Service at St Vincent's University Hospital, Dublin. This core group are supported by several departments within both Tallaght Hospital (including the Departments of Biochemistry, Endocrinology, Clinical Nutrition & Dietetics, and Radiology). Building on findings from this

thesis, several research studies have been designed and have recently commenced, or are due to commence within the next year:

1. An investigation of CT-based body composition, systemic inflammation, and QOL in chronic pancreatitis
2. A follow-up study of nutritional status and QOL following pancreatic resection
3. A national incidence and prevalence survey of chronic pancreatitis
4. Endocrine function, exocrine function, dietary intake, physical activity and QOL following an episode of severe acute pancreatitis

A national incidence and prevalence survey of chronic pancreatitis will in part address some of the limitations of the cohort studies (discussed in Chapter 5 and 6) which relate to selection and recruitment bias. The creation of a national database of chronic pancreatitis patients will, for the first time, allow the examination of the provision of services for this disease, as well as examining hospitalisation trends for pancreatitis in Ireland. This will facilitate the design of more representative cohort studies in the future.

Together with the studies that have been conducted and published to date, this research strives to improve the nutritional care of patients with acute and chronic pancreatitis.

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296. Duggan SN, Conlon, K.C. A practical guide to the nutritional management of chronic pancreatitis. *Practical Gastroenterology.* June 2013;118(Nutrition Series):24-32.

297. Duggan S, O'Sullivan M, Feehan S, Ridgway P, Conlon K. Nutrition treatment of deficiency and malnutrition in chronic pancreatitis: a review. *Nutr Clin Pract.* Aug 2010;25(4):362-370.

Appendices

Appendix A. Peer-reviewed publications arising from this thesis

Journal articles / peer-reviewed publications

1. Duggan S, Egan SM, Smyth ND, Feehan SM, Breslin N, Conlon KC. Blind bedside insertion of small bowel feeding tubes. *Ir J Med Sci.* 9 2009.

2. Duggan S, O'Sullivan M, Feehan S, Ridgway P, Conlon K. Nutrition treatment of deficiency and malnutrition in chronic pancreatitis: a review. *Nutr Clin Pract.* Aug 2010;25(4):362-370.

3. Duggan SN, O'Sullivan M, Hamilton S, Feehan SM, Ridgway PF, Conlon KC. Patients with chronic pancreatitis are at increased risk for osteoporosis. *Pancreas.* 2012;41(7):1119-1124.

4. Duggan SN, Smyth ND, O'Sullivan M, Feehan S, Ridgway PF, Conlon KC. A transatlantic survey of nutrition practice in acute pancreatitis. *J Hum Nutr Diet.* Aug 2012;25(4):388-397.

5. Duggan SN, Conlon KC. The practical management of patients with chronic pancreatitis. *Practical Gastroenterol.* 2013 June. Series 118.

6. Duggan SN, Smyth ND, McNaughton D, Murphy A, O'Keefe SJ, Conlon KC. High Prevalence of Osteoporosis in Patients with Chronic Pancreatitis: a Systematic Review and Meta-Analysis. *Clin Gastroenterol Hepatol.* 2013. *In-press*

7. Duggan SN, Conlon KC. Bone health guidelines for patients with chronic pancreatitis (Correspondence). *Gastroenterol.* 2013. *In press*

Book chapters

1. Philips M, Duggan SN, Arregui-Fresnada I, McGeeney L, Freeman K. Pancreatic Disease in Adults (Section 20). The Parenteral and Enteral and Enteral Nutrition Group of the British Dietetic Association (2013). A Pocket Guide to Clinical Nutrition. 5th Edition

Appendix B. Presentations arising from this thesis

Work arising from this thesis has been presented at national or international conferences (*invited presentation)

Oral presentations

1. *Duggan SN. Chronic Pancreatitis Symposium: Nutritional Deficiency and Enzyme Supplementation. *European-African Hepato-Pancreatico-Biliary Association Biannual Conference. Belgrade*. 2013
2. *Duggan SN. The nutritional management of patients with chronic pancreatitis. *The Irish Society for Clinical Nutrition & Metabolism.* Dublin, 2013
3. *Duggan SN. Assessing and maintaining nutritional competence in severe acute pancreatitis. *Pancreatic Society of Great Britain & Ireland – main conference.* Glasgow. 2012
4. *Duggan SN. Transatlantic survey of Dietetic practice in acute pancreatitis. *Pancreatic Society of Great Britain & Ireland- 5th Annual Nutrition Symposium. Glasgow, 2012*
5. *Duggan SN. Nutrition in Chronic Pancreatitis. *Digestive Diseases Federation*. Liverpool, 2012
6. Duggan SN, Feehan SM, O' Sullivan M, Ridgway PF, Conlon KC. Are we underestimating the risk of osteopathy in patients with chronic pancreatitis? *American Society for Enteral & Parenteral Nutrition ASPEN.* Vancouver 2011
7. Duggan SN, Egan, SM, Ridgway PF and Conlon KC (2009). Osteopathy and malnutrition are common in Irish chronic pancreatitis patients. *Pancreatic Society of Great Britain & Ireland.* Leeds, 2009. Overall prize winner

Poster presentations

1. Duggan SN, Ridgway PF, Feehan S, O'Sullivan M., Conlon KC. How do you Feed? Results from a Transatlantic Survey of Nutrition Practice in Acute Pancreatitis. *American Society for Enteral & Parenteral Nutrition ASPEN.* Vancouver 2011

2. Duggan SN, Ridgway PF, Feehan S, O'Sullivan M., Conlon KC. A delay in starting enteral nutrition results predicts requirement for PN in acute pancreatitis. *American Society for Enteral & Parenteral Nutrition ASPEN.* Vancouver 2011

3. Duggan SN, Ridgway PF, Feehan S, O'Sullivan M., Conlon KC. Serum albumin and handgrip strength are useful markers of malnutrition and nutrient deficiency in chronic pancreatitis. *Pancreatic Society of Great Britain & Ireland,* Dublin 2011

4. Duggan SN, O'Sullivan M, Feehan S, Ridgway PF, Conlon KC. Patients with chronic pancreatitis are at increased risk of osteopathy: a prospective cross-sectional study. *Trinity College Dublin, School of Medicine Postgraduate Research Day,* Dublin, 2011

5. Duggan SN, Ridgway PF, Feehan S, O'Sullivan M., Conlon KC. Osteopathy and malnutrition are common in Irish chronic pancreatitis patients. *Trinity College Dublin, School of Medicine Postgraduate Research Day,* Dublin, 2010

6. Duggan SN, Egan, SM, Ridgway PF and Conlon KC. Are CRP and BMI useful predictors of disease severity, and of length of stay in severe acute pancreatitis? *Pancreatic Society of Great Britain & Ireland.* Leeds, 2009.

Appendix C. Sample posters

How do you feed? Results from a Transatlantic Survey of Nutrition Practice in Acute Pancreatitis

Duggan SN[1,2,3], Smyth ND[1], Ridgway PF[2,3], Feehan SM[1], O' Sullivan M[4], Conlon KC[2,3]
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Introduction

Acute pancreatitis is a devastating disease in its severe form. Despite research, controversies still exist over the nutritional management of patients with severe disease. Many guidelines have been published, including ASPEN, ESPEN, the American Gastroenterology Association and the British Society of Gastroenterology, and while they broadly recommend 'early' feeding, they do not specify a time frame. Enteral feeding is unanimously recommended, however the preferred route of feeding (jejunal, gastric) is less clearly defined. There is little direction on the provision of 'additions', such as pancreatic enzymes and probiotics. Little is known regarding practice and adherence to guidelines. We conducted a survey to examine nutrition practice in acute pancreatitis in Canada, the United Kingdom (UK) and Ireland.

Objectives

We aimed to compare practice to guidelines, between specified countries and institution types.

Methods

Study design was a cross-sectional descriptive survey. Electronic surveys were sent to dietitians who see acute pancreatitis patients in the UK, Ireland and Canada. In total, 204 dietitians responded to the 37-part survey. Per country, n=117 dietitians in Canada, n=56 in the UK and n=31 in Ireland participated.

Using Minitab 15 software, chi-square analyses examined differences in categorical variables. P<0.05 was considered significant.

		University hospital	District/ General Hospital	
Severe acute pancreatitis	Feed early	52 (64.8%)	57 (48.7%)	P= 0.015*
	Feed later	27 (34.2%)	61 (51.3%)	Chi-square 5.875
Severe acute pancreatitis with obese-range BMI	Feed early	42 (53.8%)	41 (35.7%)	P=0.011*
	Feed later	36 (46.2%)	75 (64.3%)	Chi-square 6.522
Severe acute pancreatitis with pre-existing malnutrition	Feed early	69 (87.3%)	94 (78.8%)	P=0.125
	Feed later	10 (12.7%)	25 (21.2%)	Chi-square 2.275

Table 1

Comparison of timing of feeding in clinical scenarios per institution type

		Ireland	United Kingdom	Canada	Total
Enteral nutrition	Routinely	10 (32.2%)	30 (53.6%)	37 (31.6%)	77 (37.7%)
	Occasionally	19 (61.3%)	25 (44.6%)	67 (57.3%)	111 (54.4%)
	Never	2 (6.5%)	1 (1.8%)	13 (11.1%)	16 (7.8%)
Parenteral nutrition	Routinely	7 (22.6%)	7 (12.5%)	17 (17.8%)	31 (15.2%)
	Occasionally	20 (64.5%)	42 (75.0%)	88 (86.0%)	150 (73.5%)
	Never	4 (13.9%)	7 (12.5%)	12 (10.2%)	23 (11.3%)

Table 2

Reported enteral and parenteral usage in severe acute pancreatitis by country

HRB Health Research Board

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Contact: siduggan@tcd.ie

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Results

The majority of responders in all counties reported working in district/ general hospitals, with (38.9%, n=79) working in university hospitals.

When asked to identify what they consider 'early feeding', 92.8% chose <48 hours after presentation. Over half (54.2%) reported that they prefer early feeding in severe acute pancreatitis. Less responders (42%) reported that they would feed early in obesity, and more (81.9%) would feed early with pre-existing malnutrition. There was a tendency to feed earlier in university hospitals (p=0.015), especially in the obese patient (p=0.01) (see table 1).

Regarding the use of parenteral nutrition, 15.2% reported 'routine' use (table 2). Most dietitians (92.1%) reported feeding enterally at least 'occasionally', more in university hospitals than in district/ general hospitals (p=0.00).

Most dietitians reported preferring the jejunal route of feeding (64.2%), less in the UK (43.8%) than in Canada (77.8%) or Ireland (54.2%). Most (73.5%) perceive barriers to enteral feeding, most commonly medic's preference (57.8%) Reported barriers to enteral feeding are summarised in table 3.

Dieititian were asked about the provision of specific nutrient additions to enteral and parenteral fees. Results are summarised in table 4.

Are there barriers to enteral feeding in your institution?	Yes (%)	No (%)
	150 (73.5)	54 (26.5)

Please indicate what barriers there are	N	%
Medics preference	118	57.8
Technical difficulty (in placing feeding tubes)	79	38.7
Lack of practice guidelines	61	29.9
Enteral nutrition used in the past, but considered failure	18	8.8
Insufficient dietitian time	15	7.4
Dietitians preference	3	1.3

Table 3

Dietitians' perceived barriers to enteral feeding in their institutions

	Addition	Always	Sometimes	Never
Enteral nutrition	Probiotics	2 (1.1%)	25 (14.2%)	149 (84.7%)
	Pancreatic enzymes	15 (8%)	119 (63.3%)	54 (28.7%)
	Glutamine	2 (1.2%)	22 (12.8%)	147 (86%)
	Micronutrients	17 (9.9%)	64 (37.4%)	90 (52.6%)
Parenteral nutrition	Probiotics	0	8 (4.9%)	156 (95.1)
	Pancreatic enzymes	5 (3%)	35 (20.8%)	128 (76.2%)
	Glutamine	14 (8.3%)	35 (20.7%)	120 (71%)
	Micronutrients	91 (52%)	42 (24%)	42 (24%)

Table 4

Use of additions in enteral and parenteral nutrition as reported by dietitians

Conclusion

The survey underlines some deficits in the nutritional management of acute pancreatitis. Although the aim to feed early is common among dietitians, they are more likely to feed later in the obese patient. Parenteral nutrition is still widely used, and medical preference appears to be a barrier to enteral feeding.. Differences are apparent between countries; while jejunal feeding is favoured by the majority, it is used less in UK. Practice in university hospitals appears to be more compliant with guidelines than in district/ general hospitals. Although the available guidelines do not give direction on providing pancreatic enzymes with feeds, this practice is common. Despite recent negative studies, probiotics are still administered.

This study provides a platform for quality improvement interventions. It allows the tailoring of education and research to overcome barriers to optimal practice, improve adherence to guidelines and ultimately advance nutritional management in acute pancreatitis.

Serum albumin and handgrip strength may be markers of malnutrition and nutrient deficiency in chronic pancreatitis

Duggan SN[1,2,3], Ridgway PF[2,3], Feehan SM[1], O' Sullivan M[4], Conlon KC[2,3]
[1] Department of Nutrition & Dietetics, Adelaide & Meath Hospital Incorporating the National Children's Hospital, Dublin, Ireland,
[2] Centre for Pancreatico Biliary Disease, Adelaide & Meath Hospital Incorporating the National Children's Hospital, Dublin, Ireland, [3]Departments of Surgery and [4]Clinical Medicine, Trinity College Dublin,

Contact :siduggan@tcd.ie

Introduction

Malabsorption, poor intake and alcoholism contribute to poor nutritional status in chronic pancreatitis. Malnutrition and nutrient deficiency can lead to significant morbidity and a reduced quality of life. However, how best to define and assess clinical malnutrition in chronic pancreatitis has not been characterised. We investigated the occurrence and nature of malnutrition in chronic pancreatitis.

Methods

In a prospective cross-sectional study, 62 chronic pancreatitis patients and 66 matched controls were recruited. Body Mass Index (BMI, Kg/M^2)), handgrip strength (measure of functional capacity, Kg), serum albumin, C - reactive protein (CRP) and vitamins A, D and E were measured.

Results

BMI (P=0.007) and handgrip strength (P=0.048) of male patients were statistically lower than controls (table 1). Handgrip strength correlated positively with age (r=-0.431, P=0.006), and was lower in 'weight-losing' patients (P=0.016). Patients with lowest albumin were most underweight, had most severe disease and had lower vitamin levels (figures 1-3). The relationship between albumin and serum levels of vitamins A and E were independent of CRP on multivariate analysis (table 2). Vitamin D insufficiency (93.5%) was the most common vitamin deficiency, followed by vitamin E deficiency (22.6%).

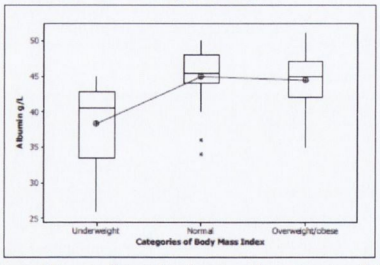

Figure 1 Serum albumin levels among the categories of BMI , ANOVA, F (2,58) = 6.38, P=0.003

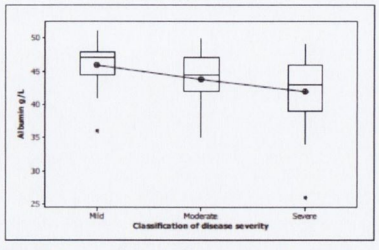

Figure 2 Serum albumin levels among the classification of disease severity, ANOVA, F(2, 58) = 4.27, P=0.019

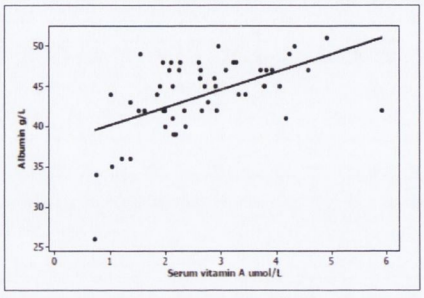

Figure 3 Correlation between serum albumin and vitamin A, Pearson's correlation 0.532, P=0.000

	Male		*P-value*	Female		*P-value*
	Patient	*Control*		*Patient*	*Control*	
BMI, mean	25.9 (4.9)	28.5 (4.2)	*0.007**	25.5 (5.4)	26.7 (3.5)	*0.422*
^Obese, n (%)	24 (53.3)	39 (81.3)	*0.038*†*	7 (41.2)	12 (66.7)	*n/a*[2]
Handgrip strength	39.9 (7.7)	43.3 (7.7)	*0.048**	25.9 (7.3)	26.3 (5.7)	*0.865*

Table 1 Backwards, stepwise linear regression showing predictors of serum albumin

Conclusion

Serum albumin showed some association with markers of malnutrition, including BMI and vitamin levels. Handgrip strength was lower in patients than in controls and was lower in patients who were actively losing weight, and in older patients. These indices could be useful markers of under-nutrition and therefore aid in the nutritional assessment of patients with chronic pancreatitis

	Coefficient	P-value
Constant	41.4	0.000
Vitamin E	0.12	0.045
Vitamin A	1.3	0.04
CRP	-0.15	0.024
Age (tertiles)	-1.89	0.026

Table 2 Backwards, stepwise linear regression showing predictors of serum albumin

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PATIENTS WITH CHRONIC PANCREATITIS ARE AT INCREASED RISK OF OSTEOPATHY: A PROSPECTIVE CROSS-SECTIONAL STUDY

Duggan SN[1,2,3], Ridgway PF[2,3], Feehan SM[1],O' Sullivan M[4], Conlon KC[2,3]
[1] Department of Nutrition & Dietetics, Adelaide & Meath Hospital Incorporating the National Children's Hospital, Dublin, Ireland,
[2] Centre for Pancreatico Biliary Disease, Adelaide & Meath Hospital Incorporating the National Children's Hospital, Dublin, Ireland ,
[3]Departments of Surgery and [4]Clinical Medicine, Trinity College Dublin,

Introduction

The economic burden of osteoporosis is immense. The total cost of osteoporotic fractures in England and Wales was £742 million in 1994[1]. Patients with chronic pancreatitis are at an increased risk of osteopathy due to malabsorption of vitamin D and calcium, poor diet, pain, alcoholism and smoking. However, there are no guidelines recommending routine bone health assessment or supplementation in chronic pancreatitis. Dujsikova *et al* reported osteopathy levels of 39% in chronic pancreatitis[2], however research is lacking. We investigated the rates of osteoporosis and osteopenia in chronic pancreatitis compared to healthy, matched controls. The aim of this study was to determine the prevalence of osteopathy in a Irish chronic pancreatitis population, and to determine predictive factors.

Methods

Fifty-three patients were recruited for this prospective, cross-sectional study, along with 58 matched-controls. Dual-X-ray Absorptiometry (DXA, bone density expressed as T-Scores below normal), smoking (expressed as 'pack years') and socioeconomic data were recorded. Regarding DXA results, we reported both the mean lowest T-score at *any area* and the mean T-score at the *right femoral neck*. Ethical approval was obtained from the Joint AMNCH/SJH ethics board.

	Patients			Controls		
Mean age#	48.7 (11.8)			48.05 (10.7)		
Upper tertile for age	57.0			56.0		
% Male	75.5			72.4		
% who finished ≥3rd level education	21			24		
	N	%		N	%	P-value
Osteoporosis	18	34		6	10.2	
Osteopenia	14	26.4		14	23.7	0.004**
Normal bone density	21	39.6		39	66.1	
	n	Mean (SD)	P-value	n	Mean (SD)	P-value
Mean T-score (lowest at any area)	53	-1.77 (1.47)		58	-0.89 (1.06)	*0.001****
Male T-score	40	-1.76(1.08)		42	-0.74 (0.98)	
Female T-score	13	-1.81 (2.36)	0.945	16	-1.28 (1.19)	0.117

Table 1. Characteristics of patients and controls, levels of osteopathy, and DXA T-scores
** Statistically significant difference with chi-square test
***Statistically significant difference with student's T-test

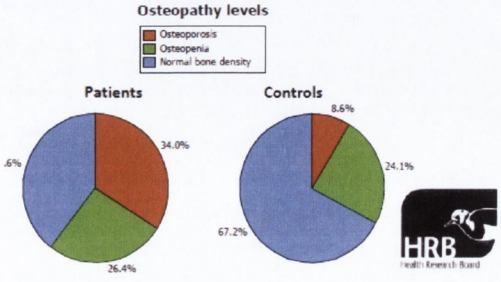

Figure 1. Comparison of osteopathy levels of patients and controls

Results

Results are summarised in table 1. Sixty percent of patients had osteoporosis or osteopenia, compared to 34.7% of controls (figure 1). The mean 'lowest T-scores' at any area were lower in patients than in controls (P=0.002), as were the T-scores at the right femoral neck (P=0.035). Patients were heavy smokers: of current and ex-smokers, the mean smoking pack-year for patients was higher than for controls (P=0.035) Patients in the highest smoking tertile had significantly lower femoral neck T-scores than those in the lowest tertile (ANOVA, P=0.007, figure 2). In a multivariate regression model, higher age, lower body mass index and heavier smoking were predictive of low bone density in patients (table 2) . In univariate analysis, patients in the highest age tertile had lower T-scores than the lowest tertile (P=0.004), but there was no difference between the sexes.

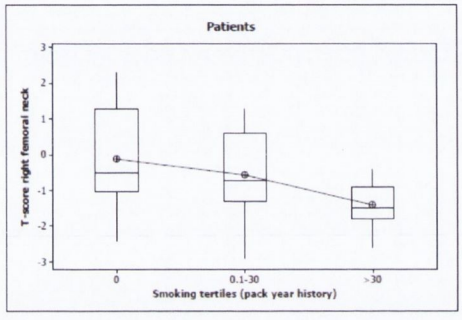

Figure 2. Box plot showing T-scores of the right femoral neck for patients according to smoking tertiles.

	Coefficient	SE coefficient	T	P
Constant	0.546	0.87	0.63	0.533
Smoking tertiles^	-0.775	0.24	-3.25	0.002
BMI categories#	0.584	0.19	3.08	0.003
Age	-0.046	0.014	-3.2	0.002

Table 2
Backward stepwise linear regression showing factors predictive of lowest T-score in chronic pancreatitis
^ Smoking tertiles are based on pack year history
#BMI groups: underweight BMI ≤20 Kg/M2; normal weight BMI 20.1-24.9; overweight BMI 25-29.9; obese or greater BMI ≥30

Conclusion

The occurrence of osteopathy in chronic pancreatitis was double that of controls. Older age, lower weight, and heavy smoking were associated with low bone density. Given the economic cost of osteoporosis, we suggest that routine bone density assessment should form part of the overall nutritional management of chronic pancreatitis. The importance of smoking cessation should be emphasised.

1. Dept of Health. Report of the advisory group on osteoporosis. London:HMSO; 1994.
2. Dujsikova H, Dite P, Tomandl J, Sevcikova A, Precechtelova M. Occurrence of metabolic osteopathy in patients with chronic pancreatitis. Pancreatology 2008;8(6):583-6.

Funded by the Health Research Board

Contact: siduggan@tcd.ie

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Osteopathy and malnutrition are common in Irish chronic pancreatitis patients

Duggan SN[1,2,3], Ridgway PF[2,3], Feehan SM[1], O' Sullivan M[4], Conlon KC[2,3]
[1] Department of Nutrition & Dietetics, Adelaide & Meath Hospital Incorporating the National Children's Hospital, Dublin, Ireland,
[2] Centre for Pancreatico Biliary Disease, Adelaide & Meath Hospital Incorporating the National Children's Hospital, Dublin, Ireland ,
[3]Departments of Surgery and [4]Clinical Medicine, Trinity College Dublin,

Introduction

Unlike other malabsorptive conditions, including Coeliac Disease and Inflammatory Bowel Disease, there are no specific, detailed nutrition or bone health guidelines for patients with Chronic Pancreatitis (CP). CP patients exhibit deterioration of exocrine function, resulting in nutrient malabsorption, and increasing the risk of malnutrition. Malabsorption of vitamin D reduces the absorption of dietary calcium, increasing the risk of low bone-mineral density (LBMD) and ultimately fracture. Studies from Eastern Europe show that the incidence of osteopathy (osteoporosis, osteopenia and osteomalacia) in CP is 39%[1].

At present, there are no formal Irish data on nutrition and bone health in this group. We commenced the first Irish study into malnutrition and bone health in CP.

Objectives

The objectives were to determine the degree of osteopathy among Irish CP patients. We sought to determine the factors that predict poor bone health among CP patients. We also compared CP patients to age and sex-match healthy controls in terms of anthropometry., smoking and alcohol.

Methods

The study was prospective and cross-sectional in design. Patients (CP group; n=49) were compared to age, sex and socio-economic-matched healthy controls (n=27; hospital employees). CP patients underwent a Dual X-ray Absorptiometry scan (DXA) to assess bone density, which is expressed as the number of standard deviations (SD) below or above the mean for age matched controls (Z-Scores). Assessment of both patents and controls included anthropometry, socio-economic data (smoking, alcohol, employment), symptoms, pain and 25(OH) Vitamin D3. Suboptimal vitamin D is defined as <80 mmol/L[2]. Student's t-test was used to compare means where appropriate. Linear regression was used to develop a predictive model for low bone density. Data were analysed using R and Minitab.

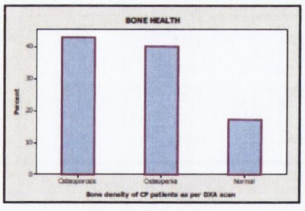
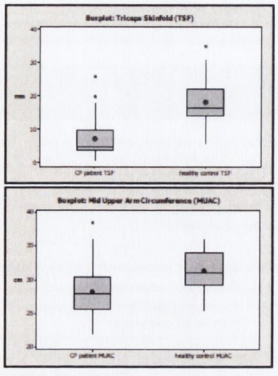


Figure 1: Rates of osteoporosis, osteopenia and normal bone density of patients with Chronic Pancreatitis using DXA



CP patients had significantly lower Triceps Skinfold compared to healthy controls

P<0.00, 95%CI (-4.87, -1.368)

CP patients had significantly lower Mid Upper Arm Circumference compared to healthy controls

P<0.00, 95%CI (-14.51, -7.5)

Figure 2: Anthropometry in CP patients vs. healthy controls

Results

Smoking and Alcohol: Only 31.7% of the CP group were 'never-smokers', compared to half of controls (47.6%). The CP group had a higher mean pack-year smoking history (16.5±16.94) than controls (9.3±13.3). Among current drinkers, CP patients had a higher alcohol intake than controls (20.6±25.7 & 10.3±9.9 units/week respectively), but this was not significant (p=0.11).

Bone Health:

82.4% of patients had osteopenia or osteoporosis on DXA scan (figure 1). 91% had suboptimal vitamin D[2]. Using linear regression (table 1), we developed a model to predict low bone density. The model shows that a high smoking history (pack year history), low BMI, and high pain score are significantly predictive of low bone density (T-Scores). Age, vitamin D levels, disease classification and education levels were not associated with bone density. The relationship between bone density and smoking (fig. 3) and bone density and pain (fig. 4) are displayed below.

Anthropometry:

Although 47% of CP patients were overweight or obese, they had lower BMI compared to controls (P=0.046). They also had lower mid upper-arm circumference (P=0.00), lower triceps skinfold (P=0.00), and among males, lower handgrip-strength (p=0.00) (figure 2).

	Coeff	lower095	ci upper095ci	Pr>|t|
(Intercept)	-4.0264	6.3242	-1.7287	0.00134
PackYr	-0.0362	-0.0619	-0.0105	0.00757
BMI	0.1286	0.0373	0.2200	0.00767
Pain	-0.3013	-0.5396	-0.0630	0.01530

Table 1: Linear Regression model shows factors predictive of a low T-Score

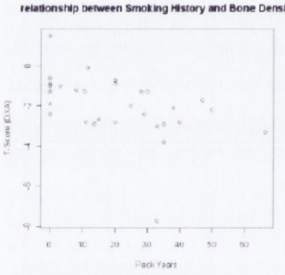


Figure 3: Plot of negative linear relationship between Smoking history (pack years) and bone density (T-Score)

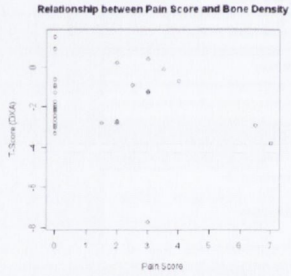


Figure 4: Plot of negative linear relationship between pain score and bone density (T-Score)

Conclusion

The level of osteopathy in this group of Irish CP patients (82.4%) far exceeds that which has been described elsewhere (39%)[1], for reasons as yet unclear. A low BMI, high smoking history and high pain scores were predictive of low bone density.

Despite the fact that many CP patients are either overweight or obese, CP patients are thinner than controls, with lower fat and muscle stores.

How best to deal with the apparently high osteopathy and vitamin D deficiency has not been tested.

1. *Dujsikova H, Dite P, Tomandl J, Sevcikova A, Precechtelova M Occurance of metabolic osteopathy in patients with chronic pancreatitis. Pancreatology 2008; 8:583-586*
2. *Heaney RP. Functional indices of vitamin D status and ramifications of vitamin D deficiency. Am J Clin Nutr 2004; 80(suppl): 1706S-9S*

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Contact: siduggan@tcd.ie

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Appendix D. Letters of ethical approval / permission

THIS NOTEPAPER MUST NOT BE USED FOR PREPARING ONE OR INVOICING PURPOSES

SJH/AMNCH Research Ethics Committee Secretariat
Dan Lynch Ph: 4142860 email: Dan.Lynch@amnch.ie
Ursula Ryan Ph: 4142342 email: Ursula.Ryan@amnch.ie
Secretariat Fax 4142371

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

Ms. Sinead Duggan
Department of Nutrition & Dietics
Adelaide & Meath Hospital
Tallaght
Dublin 24

April 3rd 2007

Re: Micronutrient Analysis of Patients with Chronic Pancreatitis Presenting to the Centre for Pancreatic Biliary Diseases, AMNCH.

Please quote this reference in any follow up to this letter: 2007/03/14 Chairman's Action.

Dear Sinead,

Thank you for your recent submission of the above study to the SJH/AMNCH Joint Research Ethics Committee.
The Chairman, on behalf of the Committee, has reviewed your study and given his ethical approval. The following documents have been reviewed:

- Patient Information Sheet and Consent Form
- Administrative Application
- Confidential Research Protocol, 2006 edition.
- Study Proposal

Yours sincerely,

Daniel R. Lynch,
Secretary,
SJH/AMNCH Research Ethics Committee

335703001

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OFFICE OF THE CHIEF EXECUTIVE OFFICER

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 414 2845
FACSIMILE +353 1 414 2896

6th August, 2008.

Ms. Sinead Duggan,
Senior Clinical Nutritionist,
AMNCH.

Dear Sinéad,

I acknowledge receipt of your request to recruit controls from AMNCH staff for your study which I note has Ethics Committee approval. I am happy to approve this and I wish you well with the study

Yours sincerely,

DR. GERRY FITZPATRICK,
ACTING CHIEF EXECUTIVE OFFICER.

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THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING SJH/AMNCH
THE NATIONAL CHILDREN'S HOSPITAL

SJH/AMNCH Research Ethics Committee Secretariat
Dan Lynch Ph: 4142860 email: Dan.Lynch@amnch.ie
Ursula Ryan Ph: 4142342 email: Ursula.Ryan@amnch.ie
Secretariat Fax 4142371

SJH/AMNCH
Research Ethics Committee

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

Ms. Sinead Duggan
Clinical Nutritionist
Department of Nutrition
Adelaide & Meath Hospital
Tallaght
Dublin 24

June 11th 2010

Please quote this reference in any follow up to this letter: 2010/06/01 Chairman's Action

Re: Survey of Nutritional Practice in Patients with Acute Pancreatitis.

Dear Sinead,

Thank you for your recent submission of the above proposal to the SJH/AMNCH Research Ethics Committee.

The Chairman, having reviewed the proposal, has given ethical approval on behalf of the Committee. He has noted that you intent to disseminate the survey in Ireland, the UK, USA, Canada, Australia and New Zealand.

Yours sincerely,

Ms. Ursula Ryan
Secretary
SJH/AMNCH Research Ethics Committee.

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

SJH/AMNCH Research Ethics Committee Secretariat
Ursula Ryan Ph: 4142342 email: □ HYPERLINK "mailto:Ursula.Ryan@amnch.ie" rsula.Ryan@amnch.ie□
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Ms. Sinead Duggan
Research Dietitian
Trinity Centre for Health Sciences
Adelaide & Meath Hospital
Tallaght
Dublin 24

July 21st 2010

Re: 2007/03/14 Chairman's Action

Please quote this reference in any follow up to this letter: 2010/25/09

Dear Sinead,

Thank you for your letter dated July 6th 2010 in which you request ethical approval for an amendment to this study.

The Chairman, on behalf of the Research Ethics Committee, having reviewed your request to add a standard bone density scan (DXA, Dual X-ray Absorpitometry) for patients and controls, has given ethical approval.

Yours sincerely

Ursula Ryan
Secretary,
SJH/AMNCH Research Ethics Committee

335703001

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THE ADELAIDE & MEATH HOSPITAL, DUBLIN
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Secretariat Fax 4142371

Ms. Sinead Duggan
1.29 Department of Surgery
Trinity Centre for Health Sciences
Education Centre
Tallaght
Dublin 24

December 7th 2011

Please quote this reference in any follow up to this letter: 2011/12/06 Chairman's Action

Re: Bone Turnover in Pancreatitis,

Dear Sinead,

Thank you for your recent submission of the above proposal to the SJH/AMNCH Research Ethics Committee.

The Chairman, having reviewed the proposal, has given ethical approval on behalf of the SJH/AMNCH Research Ethics Committee.

Yours sincerely,

Ms. Ursula Ryan
Secretary
SJH/AMNCH Research Ethics Committee

Appendix E. Template for subjects' results letters

PRINT ON HEADED PAPER

Sinead Duggan (Research Dietitian)
1.29 Dept Surgery,
Trinity Centre for Health Sciences,
AMNCH, Tallaght Dublin 24.
01 896 4173
siduggan@tcd.ie

INSERT DATE

INSERT PATIENT NAME, ADDRESS, DATE OF BIRTH, ID NUMBER

Dear **INSERT NAME**,

Thank you for attending for a nutritional assessment as a **PATIENT / CONTROL**. As explained, this was as part of our study in patients with chronic pancreatitis. The results are detailed below:

INSERT RESULT DETAILS AND FOLLOW-UP AS APPROPRIATE

Your GP will receive a copy of this letter for his/her records. Please contact your GP regarding what (if any) course of action should be taken.

Don't hesitate to contact me if you have any queries.

Kind regards,

Sinead Duggan	Professor Kevin Conlon
Research Dietitian	Consultant Pancreatic Surgeon

cc. **GP NAME AND ADDRESS**

Appendix F. 10,10,10 NJ insertion protocol

The modified 10,10,10 protocol: Centre for Pancreatico-Biliary Disease, Tallaght Hospital

1. Administer Metoclompramide* (10mg) intramuscularly or by slow intravenous injection 10 minutes prior to commencement.

   **To promote gastric emptying and thereby aid small bowel tube placement*
2. Insert an NJ fine bore feeding tube (109cm /140cm) following lubrication into the preferred nare and advance into the stomach to a predetermined length (by crude measurement against the patient prior to starting).
3. Confirm gastric placement prior to post-pyloric progression: by air auscultation initially, followed by gastric aspirate (pH <5.5). Consider other factors such as the use of proton-pump inhibitors or H_2 antagonists which may affect gastric pH.
4. When the tube was deemed to be in the stomach, advance further by increments of 5-10cm. Pull the guide-wire out of the end of the tube to determine if the tube is advancing past the pyloric sphincter: if the guide wire comes out freely, the tube is advancing, and not coiling or kinking within the gastric lumen. The tube is then advanced by another 5-10cm and this process is repeated until the tube is inserted to all but 10cm, continuously checking position by pulling the guide wire.
5. At any point if resistance is felt when pulling the guide wire, pull the NJ tube out from the nose by 5-10 cm until the guide wire is freely moving.
6. Do not flush the tube with water as by doing this the tube is lubricated internally which may result in easier removal of the guide wire which distorts the reading of the tube position.
7. When the tube is believed to be in the small bowel, seek a further aspirate (PH >6.0). Attempt to aspirate air (a further check for position) - In the case of small bowel position a 'vacuum' is usually observed, while gastric position usually yields a large volume of air.
8. Request radiological confirmation of position (plain film of the abdomen, PFA) when confident of tube position to prevent unnecessary requests.
9. For acute pancreatitis patients, the tube tip is in position if past the Ligament of Treitz.
10. For patients with tubes for reasons other than pancreatitis, the tube tip is acceptable if post pyloric.
11. The classic 'S'-shape on PFA represents the tube following the pylorus and duodenum.

1. Preliminary question

* 1. Are you involved in the nutritional care of patients with acute pancreatitis?

- ◯ Yes
- ◯ No
- ◯ Occasionally

2. Setting

1. In what type of institution do you work?

- ◯ University hospital
- ◯ District/general hospital
- ◯ Private hospital

Other (please specify)

2. Please estimate the number of beds in your institution:

- ◯ 0-200
- ◯ 201-400
- ◯ 401-600
- ◯ 601-800
- ◯ >800

3. Please estimate the percentage of your case-load dedicated to Pancreatic Disease?

4. Does your institution accept tertiary referrals for patients with pancreatitis?

- ◯ Yes
- ◯ No
- ◯ Unsure

5. Do you have a specially-dedicated multi-disciplinary team for all patients with pancreatitis?

- ◯ Yes
- ◯ No
- ◯ Unsure

6. If you have a dedicated team, is this team led by a:

- ◯ No dedicated team
- ◯ Surgeon
- ◯ Intensivist
- ◯ Other (please specify)

7. Are your patients with predicted severe acute pancreatitis routinely transferred to ICU or HDU?

- ◯ Yes
- ◯ No
- ◯ Unsure

Comment if necessary

3. Feeding practice

1. By which method does your institution classify patients for pancreatitis severity (tick all that apply)?

- ☐ (Modified) Imrie score
- ☐ APACHE
- ☐ Ranson
- ☐ Other (please specify)

2. Does your institution have a formal pancreatitis managment protocol?

◯ Yes ◯ No ◯ Don't know

* 3. Does your institution have a formal FEEDING protocol for patients with pancreatitis?

◯ Yes ◯ No ◯ Don't know

4. If yes, are you confident that this protocol is adhered to?

◯ Yes, routinely ◯ No, never ◯ Only occasionally ◯ Unsure

5. By what criteria do you decide to feed or not (tick all that apply)?

- ☐ Imrie score
- ☐ CRP (C Reactive Protein)
- ☐ Clinical parameters
- ☐ Other (please specify)

6. What cut-off for feeding would you describe as EARLY enteral feeding in severe acute pancreatitis?

Other (please specify)

* 7. In each of the following clinical scenarios, please indicate your team's management regarding TIMING OF FEEDING:

	Feed early	Feed later
Severe acute pancreatitis	◯	◯
Severe acute pancreatitis with obese-range BMI	◯	◯
Severe acute pancreatitis with pre-existing malnutrition	◯	◯

* 8. Enteral nutrition is provided to your patients with acute pancreatitis:

◯ Routinely ◯ Occasionally ◯ Never

* 9. Parenteral nutrition is provided to your patients with acute pancreatitis:

◯ Routinely ◯ Occasionally ◯ Never

10. If using Enteral nutrition routinely in acute pancreatitis, please indicate your route of choice:

	Gastric	Jejunal	Do not use enteral routinely
Feeding route	◯	◯	◯

11. If using Parenteral nutrition routinely in acute pancreatitis, please indicate your route of choice:

	Central	Peripheral	Do not use parenteral routinely
Feeding route	◯	◯	◯

* 12. For patients with severe acute pancreatitis, do you administer parenteral and enteral simultaneuosly?

◯ Routinely

◯ Never

◯ Occasionally

If occasionally, briefly describe the scenario

* 13. Are there barriers to enteral feeding in your institution

☐ Yes

☐ No

14. If yes, please indicate what the barriers are (you may choose all that apply):

☐ Medic's preference

☐ Dietitian's preference

☐ Insufficient dietitian time

☐ Other (please specify)

☐ Technical difficulty (in placing feeding tubes)

☐ Lack of practice guidelines

☐ EN used in the past, but considered failure

* 15. When calculating requirements in severe acute pancreatitis, which predictive equations do you use (you may choose more than 1)

☐ Schofield

☐ Harris-Benedict

☐ Other (please specify)

☐ Ireton-Jones

☐ 20-25 kCal/day

16. If feeding enterally in acute pancreatitis, please indicate which type of formula is used first-line:

◯ Elemental

◯ Immune-enriched

◯ Fibre-enriched

◯ Other (please specify)

◯ Standard polymeric

◯ Semi-elemental

17. What is the main factors that drive your decision of formula (you may choose all that apply)

☐ Local policy

☐ Consultant preference

☐ Availability

☐ Other (please specify)

☐ Evidence/ guidelines

☐ Cost

4. Tube insertion

* 1. If you use naso-jejunal tube feeding for acute pancreatitis in your institution, please tick the method of insertion (tick all that apply)

- [ ] Endoscopy
- [ ] Radiology
- [ ] Bedside e.g. 10,10,10 method
- [ ] Other
- [ ] Do not use naso-jejunal tubes

If other, please specify

2. If you use bedside naso-jejunal tube insertion, who places the tubes? (tick all that apply):

- [ ] Ward nurse
- [ ] Specialist nurse
- [ ] Dietitian
- [ ] Medics
- [ ] No bedside insertion

5. Additions

1. If using enteral nutrition in acute pancreatitis, do you routinely supplement with any of the following?

	Always	Never	Sometimes
Probiotics	○	○	○
Pancreatic enzymes	○	○	○
Enteral glutamine	○	○	○
Micronutrients	○	○	○

If you use any other enteral supplements, please list

2. If using parenteral nutrition in acute pancreatitis, do you routinely supplement with any of the following?

	Always	Never	Sometimes
Probiotics	○	○	○
Pancreatic enzymes	○	○	○
Parenteral glutamine	○	○	○
IV micronutrients	○	○	○

If you use any other parenteral supplements, please list

6. Discontinuing feeding

* 1. What criteria do you consider when stopping feeding in acute pancreatitis (please tick all that apply)?

- [ ] CRP
- [ ] CT
- [ ] Clinical symptoms
- [ ] Other (please specify)

* 2. What type of dietary advice do you routinely give for re-introduction of diet after recovery from severe acute pancreatitis?

- ◯ Light diet
- ◯ Do not give dietary advice
- ◯ High protein/ energy
- ◯ Low fat diet
- ◯ Low fibre diet
- ◯ Other dietary advice (please specify)

7. Guidelines

* 1. Which guidelines (if any) are you most familiar with for the nutritional treatment of acute pancreatitis?

- ◯ American Gastroenterology Association guidelines
- ◯ ESPEN guidelines
- ◯ INDI reference guide
- ◯ British Society of Gastroenterology guidelines
- ◯ Ungwars of guidelines
- ◯ ASPEN guidelines
- ◯ Other guidelines (please specify)

2. Is there any area of nutrition in acute pancreatitis that you think requires additional research or guidelines?

8. Demographics

1. Please tick your grade:

- ◯ Clinical specialist
- ◯ Senior
- ◯ Basic grade
- ◯ Manager
- ◯ Please state band if applicable

*** 2. Please state your gender**

- ◯ Male
- ◯ Female

*** 3. Please state your age-group**

- ◯ <25
- ◯ 26-33
- ◯ 34-42
- ◯ 43-51
- ◯ >52

4. How many years qualified are you?

- ◯ 0-3 years
- ◯ 4-8 years
- ◯ >8 years

9. Survey complete!

Thank you sincerely for taking the time to complete this survey.
If there is a more appropriate colleague or co-worker who could complete this survey, please forward it onto them.

Kind regards,
Sinead

1. If you wish to be contactable, please provide your name and email address (optional)

Chronic Pancreatitis Nutrition Study

ASSESSMENT 1

Completed by

Date

Patient Name: _____
PID: _____
DOB _____
Address _____
_____
_____
Or affix addressograph

Date of 1st presentation with Chronic Pancreatitis

Hospital stay in last 12 mths Y ☐ N ☐ Days ☐

Aetiology of Pancreatitis

- Alcohol ☐
- Idiopathic ☐
- Pancreas Divisum ☐
- Hereditary ☐
- Other ☐

Diagnosis of Pancreatitis

- ERCP ☐
- MRCP ☐
- CT ☐
- MRI ☐
- Other ☐

History of Pancreatic Surgery

- Resection ☐
- Drainage procedure ☐
- Other ☐

Marital Status

- Single ☐
- Married/Living with partner ☐
- Divorced/separated/widowed ☐

Education Level

- Primary ☐
- Secondary ☐
- University ☐

Smoking status

- Current Smoker (Yes / No) ☐
- Previous Smoker (Yes / No) ☐
- *Pack years ☐

*1 pack year = 20 cigarettes per day for 1 year

Employment status

- Working full-time ☐
- Working part-time ☐
- Retirement due to age ☐
- Retirement due to illness ☐
- Prolonged unemployment ☐

Co-Morbid Diseases

- Diabetes ☐
- Cardiovascular ☐
- PUD / GORD ☐
- Pulmonary ☐
- Hepatic ☐
- Renal ☐
- Other ☐

Pain status

Pain score ☐

Tests

- Faecal Elastase sent √ ☐ Date ☐ Phone ☐
- DEXA √ ☐ Date ☐ Phone ☐

Bloods sent √

- Form 1 ☐
- Form 2 ☐

Centre for Pancreatico-Biliary Diseases & Department of Nutrition & Dietetics
1

Chronic Pancreatitis Nutrition Study

ASSESSMENT 2

Completed by

Date

Patient Name:
PID:
DOB
Address
Or affix addressograph

INCLUSION CRITERIA √

Consented for study		**Included** in the study	
> 18 years		**Excluded** from the study	
No previous intestinal resections			
No IBD / Coeliac disease			

ANTHROPOMETRY

Weight Kg		IBW	
Height M		% IBW	
BMI Kg/M^2		Centile	
MUAC cm			
TSF mm			
Handgrip Kg			
Weight 1 year ago		% Weight change	

Centre for Pancreatico-Biliary Diseases & Department of Nutrition & Dietetics
2

Supplement use (Y/N)		**Details**
Sip feed		
Fat soluble vitamin		
Iron		
Calcium		
Calcium / Vitamin D		
Zinc		

Symptoms		
Steattorrhoea		
Abdominal pain		Frequency
Vomiting		
Poor appetite		
Taste disturbances		
Visual disturbances		
Other		

Pancreatic enzyme replacement therapy

Yes ☐ No ☐

Amount per day (units)

Other medications

Oral hypoglycaemic agents	Yes		No	
Insulin	Yes		No	
Analgesic agents	Yes		No	
Laxatives	Yes		No	
H2 Blockers / PPI	Yes		No	
Others	Yes		No	

Type and dosage of pain relief

Alcohol consumption

Never drinker

Ex-drinker

Current drinker

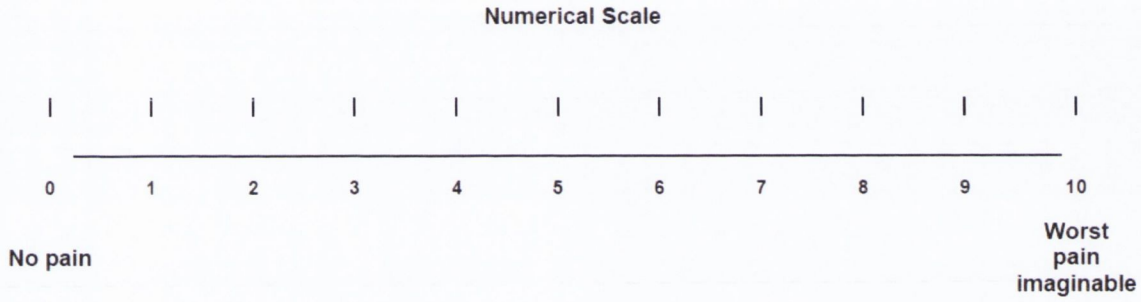
Units per week

BIOCHEMISTRY

	NORMAL	RESULT	COMMENT
Vitamin A			
Vitamin E			
Vitamin D			
Zinc			
Copper			
Vitamin B12			
Folate			
Hb			
Iron			
TIBC			
Transferrin sats			
WCC			
CRP			
PTH			
Amylase			
HbA1C			
Glucose			
Albumin			
Alk Phos			
GGT			
ALT			

Appendix J. Chronic pancreatitis pain scale

PAIN SCALE
Please indicate your level of pain today



Appendix K. Data extraction form for systematic review

Articles identified from initial search

RESEARCHER

DATE OF EXTRACTION
(e.g. 1st Oct 2012)

STUDY ID

RECORD NUMBER
(e.g. NS001, SD017)

AUTHOR
(e.g. Smyth ND et al)

ARTICLE TITLE
(Full title)

CITATION
(Full reference)

TYPE
E.g. Journal article, conference abstract

STUDY DESIGN
E.g. Case-series

POPULATION
E.g. Severe chronic pancreatitis

OUTCOME MEASURED
E.g. Bone density (DXA)

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✸
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✸
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✸
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✸
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview where blind to case/control status ✸
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✸
   b) no

3) Non-Response rate
   a) same rate for both groups ✸
   b) non respondents described
   c) rate different and no designation

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✸
   b) somewhat representative of the average _____ in the community ✸
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview ✸
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✸
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

The JAMA Network

From: **Meta-analysis of Observational Studies in Epidemiology: A Proposal for Reporting**

JAMA. 2000;283(15):2008-2012.
doi:10.1001/jama.283.15.2008

Date of download: 11/03/2012

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Table. A Proposed Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies

Reporting of background should include
Problem definition
Hypothesis statement
Description of study outcome(s)
Type of exposure or intervention used
Type of study designs used
Study population
Reporting of search strategy should include
Qualifications of searchers (eg, librarians and investigators)
Search strategy, including time period included in the synthesis and keywords
Effort to include all available studies, including contact with authors
Databases and registries searched
Search software used, name and version, including special features used (eg, explosion)
Use of hand searching (eg, reference lists of obtained articles)
List of citations located and those excluded, including justification
Method of addressing articles published in languages other than English
Method of handling abstracts and unpublished studies
Description of any contact with authors
Reporting of methods should include
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results
Assessment of heterogeneity
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated
Provision of appropriate tables and graphics
Reporting of results should include
Graphic summarizing individual study estimates and overall estimate
Table giving descriptive information for each study included
Results of sensitivity testing (eg, subgroup analysis)
Indication of statistical uncertainty of findings
Reporting of discussion should include
Quantitative assessment of bias (eg, publication bias)
Justification for exclusion (eg, exclusion of non–English-language citations)
Assessment of quality of included studies
Reporting of conclusions should include
Consideration of alternative explanations for observed results
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)
Guidelines for future research
Disclosure of funding source

Appendix N. Sample letter for participation in bone metabolism study

DATE

NAME

Dear X

I am writing to you because you had a previous admission to Tallaght Hospital with chronic pancreatitis and I wish to **invite you to participate in a study on bone health in patients with chronic pancreatitis.**

In the past few years, I have been doing research in nutrition in chronic pancreatitis, and in particular **bone health.** From our previous study of 62 patients with chronic pancreatitis, we found that the majority have either **osteoporosis (brittle bones) or osteopenia (thinner bones)**. To better understand this, we are recruiting for the second phase.

This will **involve the following**:

- A DXA scan (to assess your bone density, quick and painless - similar to an xray)
- A blood test and possibly a urine sample (to measure vitamin D and other bloods to measure bone formation/ breakdown, and inflammation)
- Weight, height, Body Mass index, questions on smoking and alcohol history
- FRAX questionnaire to assess your risk of a bone fracture

This would all take place in **one appointment, except for the DXA scan** which would be arranged on an evening in the X-ray dept. We would ask you to come for a morning appointment (fasting) and we would explain the project to you in more detail.

This project is being done as part of my **research towards and PhD** and by doing this we hope to improve the knowledge about chronic pancreatitis and ultimately improve the service to patients, both in Ireland and internationally.

All the tests will be **free of charge** (paid for in part by a grant from the Health Research Board). To get the DXA scan privately can cost up to 150 Euro and some of the blood tests can cost almost 50 Euro.

If you are interested in attending the appointment, please call 01 896 4173, or email *bonepancreas@gmail.com* (preferable).

Appointments are likely to be Monday or Friday mornings.

Kind regards,

Sinéad Duggan

Research Dietitian
Trinity Centre for health Sciences,
Tallaght Hospital

Prof Kevin Conlon

Consultant Surgeon
Trinity College
Tallaght Hospital

Appendix O. Subject suitability form for bone metabolism study

Subject suitability screening form
Bone turnover in pancreatitis study

Recruited as patient ☐ control ☐

Confirm subject is adult, >18 years of age ☐

For patients

Does patient have a diagnosis of chronic pancreatitis? ☐

How was this diagnosis made?

_____

Referring consultant

_____

Checklist *

- ☐ Was this subject recruited in phase 1 (check list)
- ☐ Is this subject on medication which could affect bone turnover?
- ☐ Has this subject had a major gastro-intestinal resection?
- ☐ Does this subject have any malabsorptive condition (coeliac disease, inflammatory bowel disease)?
- ☐ Does subject have cystic fibrosis?
- ☐ Does subject have pancreatic cancer?
- ☐ Is subject pregnant?
- ☐ Does subject have a prognosis of <6 months

**Not eligible if yes to these questions*

Eligible for study ***Yes*** ☐ ***No*** ☐

Sinead Duggan January 2012
Page 1 of 1

FRONT SHEET

Assessment form

Bone turnover in pancreatitis study

Date ___/ ___/ 201 __ **Completed by**

Recruited as patient ☐ **control** ☐

Affix addressograph or print name/ MRN. DOB/ address

Informed consent obtained ☐

Checklist *

- ☐ Urine sample obtained
- ☐ Sent for bloods
- ☐ Weight, height, BMI
- ☐ Alcohol intake and smoking history
- ☐ FRAX

Page 2

Date ___/ ___/ 201 __ **Completed by**

Recruited as patient ☐ **control** ☐

Affix addressograph or print name/ MRN. DOB/ address

Weight
Kg to nearest 0.1, light clothes, no shoes

Height
M to nearest 0.1, no shoes

Body mass index
Weight (Kg) / Height (M)^2

Alcohol

Current drinker
Ex-drinker
Never drinker

How many drinks per day or per week? Types? Frequency?

_____

Units per week:

_____

Page 3

Date ___/___/201__ **Completed by**

Recruited as patient ☐ **control** ☐

Affix addressograph or print name/ MRN. DOB/ address

Smoking

Current smoker
Ex-smoker
Never smoker

How many per day or per week? For how many years?

_____

Pack year history

_____

Page 4

Date ___/___/201__ **Completed by**

Recruited as patient ☐ **control** ☐

Affix addressograph or print name/ MRN. DOB/ address

FRAX (Record the following – complete online)

Age / DOB
Sex
Weight
Height

☐ Previous fracture
☐ Previous fractured hip
☐ Current smoking
☐ Glucocorticoid use
☐ Rheumatoid arthritis
☐ Secondary osteoporosis
☐ Alcohol > 3 units per day

Femoral neck BMD g/cm^3 _____ (from DXA scan)