The epidemiological, clinical and genetic aspects of chronic pancreatitis in Ireland

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Summary

Chronic pancreatitis is a progressive, inflammatory and malabsorptive disease of the pancreas which considerably affects a patient's health and quality of life. Chronic diseases such as chronic pancreatitis impact greatly on the healthcare system. Patients with chronic pancreatitis can expect to have multiple encounters with healthcare services to manage symptoms and comorbidities associated with the disease. Chronic pancreatitis patients require complex, multidisciplinary care, in a number of healthcare settings. One of the principle factors that motivated these studies is that chronic pancreatitis is poorly understood by health professionals outside of specialist centres. Lack of acumen among non-specialists can lead to reactive, rather than proactive treatment of disease sequelae. Thus, the overarching aim of this thesis was to examine the management of chronic pancreatitis in Ireland.

Four broad objectives were identified as follows;

- To examine the practice of managing chronic pancreatitis in Ireland
- To investigate the prevalence of chronic pancreatitis in Ireland
- To investigate the occurrence of small bowel intestinal overgrowth (SIBO), a common cause of malabsorption in chronic pancreatitis
- To examine the prevalence of major pancreatic gene mutations in Irish chronic pancreatitis patients

Four interrelated studies were designed to fulfil the thesis objectives.

The first study examined the management of chronic pancreatitis in two prominent settings in Ireland through two surveys, one of hospital-based specialists, and one of general practitioners in primary care. Results from these studies highlighted deficits in the management of chronic pancreatitis in both primary and secondary care, and also emphasised a number of important areas for potential improvement. One deficit which was identified by the surveys was the lack of available guideline for the management of

chronic pancreatitis in primary care. As a direct outcome of the surveys, primary care guidelines for the management of chronic pancreatitis were developed, which comprised part C of chapter 6.

An assessment of the epidemiology of chronic pancreatitis in Ireland followed, undertaken through an analysis of the Hospital Inpatient Enquiry system. The discharge prevalence of chronic pancreatitis in Ireland was 11.6-13.0 per 100,000 of population between 2009 and 2013 inclusive. A systematic review was then undertaken, which suggested that the prevalence, incidence and hospitalisation of chronic pancreatitis are increasing worldwide, though sparsely reported. The prevalence in Ireland was found to be similar to the prevalence in a small number of studies which utilised similar methodologies.

The third study examined an important, frequently overlooked, and poorly understood aspect of the management of chronic pancreatitis. An analysis of 35 non-surgical patients with pancreatic exocrine insufficiency, and 31 healthy controls found a SIBO prevalence of almost 15% amongst chronic pancreatitis patients and 0% in controls. A positive SIBO result was associated with alcohol aetiology, the use of acid-suppression medication, pancreatic enzyme replacement therapy, diabetes, and unintentional weight loss. Treatment of SIBO in the cohort resulted in symptom improvement in all patients. This study provided evidence for the management of a condition which is frequently overlooked and poorly understood.

The fourth study investigated the prevalence of major pancreatic gene mutations in chronic pancreatitis patients, the presence of which are thought to increase disease risk. This study revealed the presence of common pancreatic mutations in almost 18% of patients. The presence of mutations confers an almost four-fold higher risk amongst chronic pancreatitis patients, which is clinically significant. The presence of *SPINK1* mutation N34S, considered to be a disease modifying mutation, was particularly enriched in chronic pancreatitis patients, conferring an almost 5-fold increased risk of

disease. The introduction of routine genetic screening may be seen as a critical aspect of the aetiology-based diagnosis and is important to future disease management. Together, these data will ultimately improve the management of patients with chronic pancreatitis.

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Go raibh mile maith agaibh go léir

Peer reviewed publications arising from this thesis

Journal articles / peer-reviewed publications

1. **Ní Chonchubhair HM**, O'Shea B, Kavanagh DO, Ryan BM, Duggan SN, Conlon KC. Chronic pancreatitis in primary and hospital based care in Ireland: the management of an orphan disease. *JOP Journal of the Pancreas.* 2016
2. **Ní Chonchubhair HM**, Bashir Y, McNaughton D, Barry JM, Duggan SN, Conlon KC. Hospital discharges and patient activity associated with chronic pancreatitis in Ireland 2009-2013. *Pancreatology.* 2017 17(1):56-62. PMID: 27916415
3. **Ní Chonchubhair HM**, Bashir Y, Dobson M, Ryan BM, Duggan SN, Conlon KC. The prevalence of small intestinal bacterial overgrowth in non-surgical patients with chronic pancreatitis and pancreatic exocrine insufficiency (PEI). *Pancreatology.* 2018
4. Duggan SN, **Ní Chonchubhair HM**, Lawal O, O'Connor DB, Conlon KC. Chronic pancreatitis: a diagnostic dilemma. *World J Gastroenterol.* 2016 22(7): 2304-2313. PMID: 2690029
5. Memba R, Duggan SN, **Ní Chonchubhair HM**, Griffin O, Bashir Y, O'Connor DB, Murphy A, McMahon J, Volcov Y, Ryan BM, Conlon KC. The potential risk of gut microbiota in pancreatic disease: a systematic review. *Pancreatology.* 2017 17(6): 867-874. PMID: 28935288
6. O' Connor DB, **Ní Chonchubhair HM**, Duggan SN, Conlon KC. Clinical Focus: Pancreas exocrine insufficiency. Hospital Doctor of Ireland. May 2015; Vol 21 No 4.

Presentations arising from this thesis

INTERNATIONAL

Oral presentation

1. Ní Chonchubhair HM. Small intestinal bacterial overgrowth in chronic pancreatitis patients with pancreatic exocrine insufficiency: a prospective cohort study. *European-African Hepato-Biliary Association Biannual Conference, Mainz, Germany.* 2017

Poster presentation

1. Ní Chonchubhair HM, Bashir Y, Dobson M, Ryan BM, Duggan SN, Conlon KC. Small intestinal bacterial overgrowth in chronic pancreatitis patients with pancreatic exocrine insufficiency: a prospective cohort study. *British / Irish Gastro (BIG) Meeting.* 2017, Belfast, United Kingdom.
2. Ní Chonchubhair HM, Bashir Y, Dobson M, Ryan BM, Duggan SN, Conlon KC. Small intestinal bacterial overgrowth in chronic pancreatitis patients with pancreatic exocrine insufficiency: a prospective cohort study – preliminary results. *Pancreatic Society of Great Britain & Ireland Annual Conference.* 2016, Manchester, United Kingdom.
3. Ní Chonchubhair HM, Duggan SN, Conlon KC. The first report of chronic pancreatitis prevalence in Ireland–preliminary results. *Pancreatic Society of Great Britain & Ireland Annual Conference.* 2015, Manchester, United Kingdom.
4. Ní Chonchubhair HM, O'Shea B, Duggan SN, Conlon KC. Chronic pancreatitis in primary care: the management of an orphan disease. *Pancreatic Society of Great Britain & Ireland Annual Conference.* 2015, Norwich, United Kingdom.
5. Ní Chonchubhair HM, Kavanagh DO, Duggan SN, Conlon KC. Chronic pancreatitis in Ireland: the management of an orphan disease. *European Pancreas Club.* 2015, Toledo, Spain.

NATIONAL

Oral presentation

1. Ní Chonchubhair HM. Small intestinal bacterial overgrowth in chronic pancreatits patients with pancreatic exocrine insufficiency: a prospective cohort study. *Sylvester O'Halloran Surgical Scientific Symposium.* 2017, Limerick.
2. Ní Chonchubhair HM. Small intestinal bacterial overgrowth in chronic pancreatitis patients with pancreatic exocrine insufficiency: a prospective cohort study. *Sir Peter Freyer Memorial Lecture and Surgical Symposium.* 2017, Galway.
3. Ní Chonchubhair HM. Chronic pancreatitis in primary and hospital-based care in Ireland: the management of an orphan disease. *Sir Peter Freyer Memorial Lecture and Surgical Symposium.* 2016, Limerick.
4. Ní Chonchubhair HM. Chronic pancreatitis in primary care. *Joint AUDGPI/ICGP Scientific Meeting.* 2016, Dublin.

Poster presentation

1. Ní Chonchubhair HM, Basir Y, McNaughton D, Duggan SN, Conlon KC. The prevalence of chronic pancreatitis in Ireland does not appear to be due to alcohol in Ireland –preliminary results. *Sylvester O'Halloran Memorial Lecture and Surgical Symposium.* 2016, Limerick
2. Ní Chonchubhair HM, Duggan SN, Conlon KC. The first report of chronic pancreatitis prevalence in Ireland. *Irish Society of Gastroenterology Meeting.* 2015, Dublin *(1st Prize Poster Winner)*
3. Ní Chonchubhair HM, Kavanagh DO, Duggan SN, Conlon KC. Chronic pancreatitis in Ireland: the management of an orphan disease. *Irish Society of Gastroenterology Meeting.* 2015, Dublin

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Abbreviations

25-OH-D	25, hydroxyvitamin D
α-cells	Alpha cells
ACHI	Australian Classification of Health Interventions
ACS	Australian Coding Standards
AGA	American Gastrointestinal Association
AMNCH	Tallaght Hospital
ANOVA	Analysis of variance
ARDS	Acute respiratory distress syndrome
A&E	Accident and Emergency
β-cells	Beta cells
BMD	Bone mineral density
BMI	Body mass index
C	Celsius
CASR	Calcium sensitive receptor
CFTR	Cystic fibrosis transmembrane conductance regulator
CI	Confidence interval
CL	Chloride
CME	Continuing medical education
CPA1	Carboxypepsidase-1
CRP	C-reactive protein
CSO	Central statistics office
CT	Computed tomography
CTRC	Chymotrypsin C
DM	Diabetes mellitus
DRG	Diagnosis related group
DXA	Dual-energy x-ray absorptiometry
EDTA	Ethelynediaminetetraacetic acid
EMR	Electronic Medical Record
ERCP	Endoscopic retrograde cholangiopancreatography
ESRI	Economic and Social Research institute
FE-1	Faecal Elastase-1
GI	Gastrointestinal
GLP-1	Glucagon-like polypeptide-1
GMS	General Medical Scheme
GP	General Practitioner
GWAS	Genome wide association study

HbA1c	Haemoglobin A1c
HCO_3	Bicarbonate
HIPE	Hospital inpatient inquiry
HIU	Health Intelligence Unit
HPO	Health Pricing Office
HRB	Health Research Board
HSE	Health Service Executive
IAPP	Insulin amyloid polypeptide-A
ICD	International Classification of Disease
ICGP	Irish College of General Practitioners
ICS	Irish Coding Standards
ISG	Irish Society of Gastroenterology
IU	Insulin units
JREC	Joint research ethics committee
K86.0	Alcohol induced chronic pancreatitis
K86.1	Other aetiology chronic pancreatitis
MDT	Multidisciplinary team
MMC	Migrating Motor Complex
MRCP	Magnetic resonance cholangiopancreatography
N	Sample size
NCCH	National Centre for Classification of Health
NAPS2	North American Pancreatitis Study-2
NPRS	National perinatal reporting system
NS	Not significant
OECD	Organisation for Economic Cooperation & Development
OPD	Outpatient department
P	P-value
PaSC	Pancreatic stellate cells
PEI	Pancreatic exocrine insufficiency
PERT	Pancreatic enzyme replacement therapy
PPI	Proton pump inhibitor
PPM	Parts per million
PFA	Plain film of abdomen
PRSS1	Cationic trypsinogen
QIP	Quality In Practice
QOL	Quality of life
QRG	Quick Reference Guide
RCIPD	Research committee of intractable pancreatic diseases

RCSI	Royal College of Surgeons Ireland
RCT	Randomised controlled trial
SAPE	Sentinel Acute Pancreatitis event
SD	Standard deviation
SE	Standard error
SHO	Senior house officer
SIBO	Small intestinal bacteria overgrowth
SIRS	Systemic inflammatory response syndrome
SJH	St James's Hospital
SPSS	Statistical Package for Social Sciences
SPINK1	Serine Protease Inhibitor Kazal type 1
SR	Systematic review
SVUH	St Vincent's University Hospital
Ųg/g	Microgram / gram
U	Units
UK	United Kingdom
US	Ultrasound
USA	United States of America
WHO	World Health Organisation
X^2	Chi-squared statistic

1. Chapter 1– Thesis introduction

1.1. Introduction to the thesis

In recent years there has been a dramatic shift in the population age profile, with the world's population growing rapidly in combination with an increasing life expectancy (1). Advancements in healthcare combined with an aging population have led to growing numbers of people surviving with compound chronic diseases that may, in former times have resulted in death. Further to this, the proportion of people suffering with one, or multiple chronic diseases is also swiftly increasing due to accumulated lifetime exposures to disease associated risk factors (2). The implications of acquiring progressively and vastly more complex-to-manage chronic diseases for healthcare systems, and society as a whole are momentous (3). The need for change in current healthcare systems to respond to these real-time challenges is unquestionable. How we as a society deal with the growing burden of chronic diseases in often exceedingly vulnerable sectors of society is an enormous challenge. Chronic diseases essentially entail a myriad of associated health, social and socioeconomic consequences and rarely require treatment and management in isolation. Chronic pancreatitis represents a classic example of an environment exposure and genetic risk-associated chronic disease that has substantial implications for patients, their families and the wider community.

Pancreatitis refers to a condition of inflammation of the pancreas, which may occur in acute, recurrent acute or chronic form. Acute pancreatitis due to its urgent nature requires immediate hospitalisation for treatment and normalisation of symptoms. The chronic form, chronic pancreatitis, is characterised by progressive and life-limiting symptoms which requires long-term healthcare and interaction with healthcare services. Data indicate that acute pancreatitis may progress to recurrent acute pancreatitis and then to chronic pancreatitis in a disease continuum (4). Glandular

damage from recurrent episodes of acute pancreatitis can lead to irreversible changes which are characteristic of chronic pancreatitis. Chronic pancreatitis impacts considerably on patients' nutritional status, endocrine status, bone health, and comorbidity, and constitute a significant healthcare system resource burden. Like all chronic diseases, the consequences for patients, their families and the wider community are many. Managing chronic diseases imposes significant costs to all levels of society, and strategies are now aimed at improving disease prevention, health promotion and increasing the availability of appropriate and effective healthcare for all patients. As a chronic disease the epidemiological burden of chronic pancreatitis is incompletely understood. In fact, the diagnosis of chronic pancreatitis is difficult due to non-specific gastrointestinal (GI) symptoms, and a definitive diagnosis relies on the presence of irreversible morphological pancreatic dysfunction which is rarely present in early disease. Therefore, diagnosis is a challenge in early disease, and patients may be wrongly diagnosed for many years.

Characteristically, as the disease progresses, chronic pancreatitis patients suffer multiple disease-associated co-morbidities which further complicate care. Fibrosis of the pancreas is often accompanied by fat malabsorption, secondary diabetes, and an increased risk of pancreatic cancer (5, 6). Patients with chronic pancreatitis have a shorter survival than the general public, and may progress to pancreatic cancer with a pooled relative risk of 13.3 (7). The available earlier reports on chronic pancreatitis mortality included small cohorts of patients limiting statistical precision (8-10). A recent nationwide study conducted in Denmark demonstrated that chronic pancreatitis patients had a 5-fold higher increased risk of death compared with age-and sex-matched controls, with mortality associated with pancreatic cancer and extra-pancreatic consequences of disease (11). Pancreas exocrine insufficiency (PEI), which is known to occur in up to 87% of patients (12) is a significant independent risk factor for mortality in chronic pancreatitis patients (13). Pancreatic cancer is one of the most

aggressive malignancies and patients are thought to have a dismal 5-year survival rate of approximately 8% (14). Determining which chronic pancreatitis patients develop what complications, how quickly they will advance, and what the most effective interventions are is currently unclear. These are rate limiting factors in the management of this complex disease and the ability to inform patients of disease course. Chronic pancreatitis is associated with substantial disease-related morbidity which profoundly impacts on patients' lives and the health system as a whole. Considering the disease burden associated with chronic pancreatitis, there is need to improve understanding of the disease in order to develop a strategic approach to patient management, service planning and resource allocation. Although guidelines have been published, there are no systematic guidelines directing the multidisciplinary approach to achieve uniformity of excellence in patient care (15). Therefore, there are considerable research gaps that must be addressed to improve patient outcomes and reduce mortality.

Disease represents the end-point of a process of alteration to biological systems, and epidemiological research helps to elucidate the spectrum of disease resulting from many agents and conditions. The number of studies worldwide examining the population distribution of chronic pancreatitis is surprisingly scarce. Certainly no Irish data are available on the epidemiology and true population-based burden of this disease, and in fact there are no National UK studies, and only regional studies from the US. Epidemiological data in chronic pancreatitis are required to generate information for health professionals to develop, implement and evaluate effective interventions for the prevention of disease and health promotion. Data are also fundamental to enable healthcare policy makers make appropriately informed decisions regarding resource allocation and service development.

Moreover, little is known about how well the disease is managed in Ireland or internationally, and the small numbers of available studies have indicated that the management principles differ significantly between countries. Although chronic

pancreatitis cannot be diagnosed in primary care, (it requires hospitalisation for certain areas of management), it may be manged long-term in primary care with integrated management from outpatient and hospital-based care. However, little is known about the availability of chronic disease management programmes for chronic pancreatitis, and services are presumed to be potentially limited in some geolocations. While research for many areas of chronic pancreatitis is scarce, where practice guidelines do exist, health professional adherence is unknown.

This thesis describes four studies designed to describe the epidemiology and management of chronic pancreatitis in Ireland; (1) the management of chronic pancreatitis in two prominent healthcare settings in Ireland, (2) an investigation of the epidemiology of chronic pancreatitis and contextualising Ireland amidst available epidemiological reports worldwide, (3) the prevalence of small intestinal bacterial overgrowth (SIBO), a malnutrition related complication in chronic pancreatitis, and (4) an investigation of major pancreatic gene mutations in the chronic pancreatitis cohort.

Chapter 1 provides an overview of the pancreas and pancreatitis; Chapter 2 discusses the available literature pertaining to important aspects of chronic pancreatitis discussed in this thesis; Chapter 3 outlines the context, rationale and aims that underpin this work; Chapter 4 describes the methodological considerations. Chapters 5 to 8 describe the four empirical studies in the thesis which are tied to the study objectives. The thesis concludes with a discussion of key findings in Chapter 9, in the context of clinical and theoretical implications. This chapter also discusses some of the methodological considerations as well as future research directions.

1.2. Introduction to the pancreas

1.2.1. Anatomy and histology of the pancreas

The pancreas is an elongated, tapered, glandular organ which is located in the retroperitoneum, extending across the posterior abdominal wall from the second part of the duodenum to the spleen. The pancreas is a soft, flattened organ that measures about 12.5-15cm (4.5-6in.) in length and consists of a head, body and tail (16). The head of the pancreas is encircled by the duodenum and the body forms the main bulk of the organ that ends in a tail which lies in contact with the spleen. The pancreas is an un-encapsulated organ that is classified as a heterocrine gland, as it contains both exocrine and endocrine glandular tissue. The arterial blood supply to the pancreas is from two major arteries supplying the abdominal organs, the celiac and super mesenteric arteries. Venous drainage from the pancreas is *via* the splenic vein and superior mesenteric vein, draining into the portal vein, with the splenic vein running along the body of the pancreas (16). The pancreas plays a pivotal role in digestion (exocrine pancreas), in glucose homeostasis and in the control of upper GI motility and function (endocrine pancreas). Innervation of the pancreas is controlled by the parasympathetic and sympathetic nervous system. Approximately 98% of pancreatic cells are arranged in clusters called acini; these cells produce digestive enzymes which flow into the gastrointestinal tract from the pancreatic tail through a network of ducts (16). An acinus is made up of approximately 40 acinar cells which are connected by centroacinar cells to the pancreatic duct system lined by pancreatic duct cells (17). Approximately only 2% of the pancreas is comprised of endocrine tissue, which is scattered in 1-2 million tiny clusters among the exocrine acini and are called pancreatic islets of the islets of Langerhans (16). These islets contain approximately 3,000-4,000 cells which secrete their hormones into adjacent fenestrated capillaries (17) (Figure 1.2).

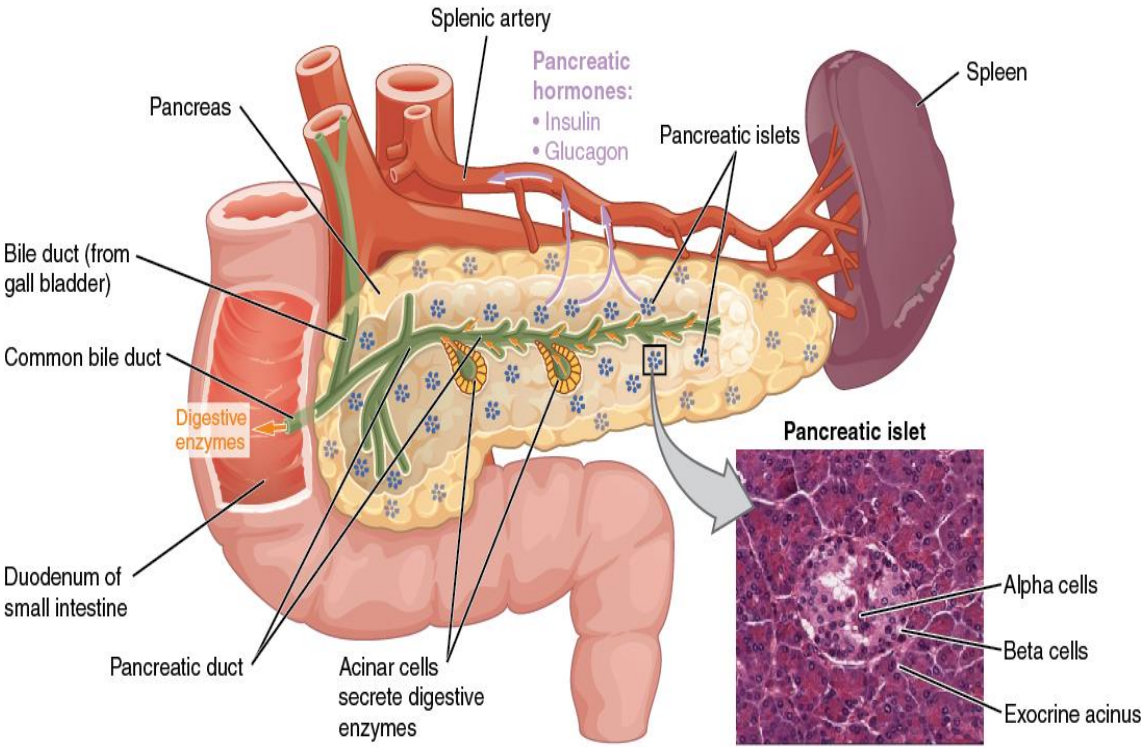

Figure 1.1: The pancreas anatomy and islet cells

(Reproduced with permission from (18))

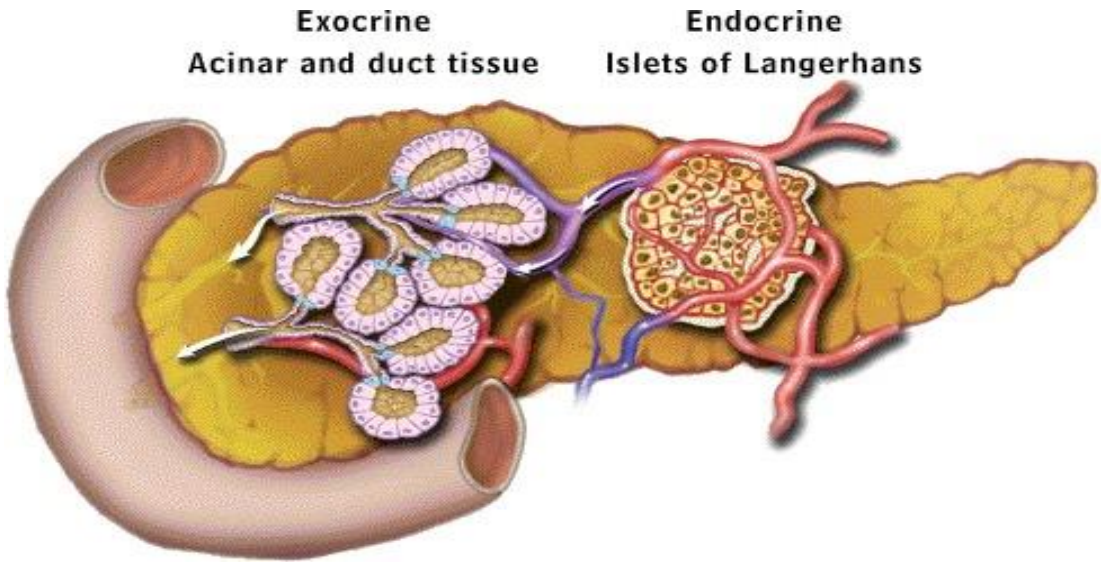

Figure 1.2: The exocrine and endocrine pancreas.

The pancreas consists of exocrine portion (acinar and duct tissue) and endocrine portion (islets of Langerhans). The exocrine pancreas cells secrete digestive enzymes, water and bicarbonate (HCO_3) into the duodenum. The endocrine pancreas secrete hormones into the blood stream

(Adapted with permission (19))

Drainage of the exocrine secretions is through the main pancreatic duct which has many tributary ductules and it extends close to the posterior surface that gradually tapers towards the pancreatic tail. The main pancreatic duct (duct of Wirsung) usually joins the common bile duct from the liver and gallbladder to penetrate the duodenum as a single duct called the hepatopancreatic ampulla (ampulla of Vater). Most people have a pancreatic duct but in some people a second duct exists (duct of Santorini) which may be functional or non-functional, and may open separately into the second part of the duodenum (20). The exocrine secretions from the acinar cells (referred to as pancreatic juice) enter the duodenum via the main and accessory pancreatic ducts, while the endocrine secretions from the islets enter the blood stream. Although the exocrine and endocrine pancreas systems are distinct, there are important inter-relationships between both. The capillaries of the exocrine tissue that surrounds the islets are perfused by blood flow from the endocrine pancreas, prior to entry into general circulation (21). However, the effect of this is incompletely understood, but it is thought that the pancreatic acinar cells contain insulin receptors which are involved in exocrine pancreas digestive enzyme synthesis (19).

1.3. Exocrine pancreas

The pancreas is the most metabolically active organ in the body which produces approximately 1 to 2.5 litres of pancreatic secretions each day in the form of colourless, alkaline and iso-osmotic pancreatic juice (17). This juice consists of inorganic components such as water, potassium, chloride, bicarbonate and several enzymes. Pancreatic juice contains hydrolytic enzymes for the digestion of complex carbohydrates, proteins and lipids. Most important of these enzymes are α-amylase, trypsin, chymotrypsin and lipase. The functional unit of the exocrine pancreas consists of the acinus and its drainage ductule, which connects the acinus lumen to the

duodenum. The ductules drain in to intercalated ducts which then drain into the main pancreatic duct. The role of the acinus is to synthesise, store and secrete digestive enzymes. The acini of the pancreas are comprised of zymogenic cells where digestive enzymes are stored in inactive precursor forms inside acidic zymogen granules in the apical region, preventing pancreatic auto-digestion and inflammation as enzymes only become active after reaching the duodenum. The basolateral membranes contain receptors for hormones, and neurotransmitters which stimulate enzyme release (22) and in their basal cytoplasmic domain there is abundant rough endoplasmic reticulum (20). The acinar cells are lined by epithelial cells which secrete bicarbonate-rich fluid. Both duct and acinar cells are polarised epithelial cells and secrete into the duct across their apical cell membrane (23).

Another important resident cell that plays a key role in major disorders of the exocrine pancreas are pancreatic stellate cells (PaSCs) (20). Their role in normal exocrine function is to lay down basement membrane to direct the correct formation of epithelial structures (19). In diseases such as chronic pancreatitis, the PaSC are transformed into proliferating myofibroblastic cells that synthesise and secrete extracellular matrix proteins, proinflammatory cytokines and growth factors (19). The actions of the mutated form of PaSC are thought to be central to the inflammation and fibrosis that occurs in chronic pancreatitis and are procarcinogenic for pancreas cancer. The mutated myofibroblastic transformed state of PaSC is emerging as a key participant in both the rate of growth of pancreatic cancer and chemotherapy resistance (19).

1.3.1. Digestion of nutrients

Intraluminal digestion of large molecular nutrient particles represents the basic requisite for optimum digestion and absorption of nutrients and is guaranteed by a finely balanced interplay among motor and secretory functions of the GI tract (17, 24). The digestion of macronutrients is a pre-requisite to absorption which occurs *via* a process

of enzymatic hydrolysis. Pancreatic enzymes especially lipase, amylase, trypsin and chymotrypsin are fundamental to this process. Additionally, several enzymes of the brush border combined with other pancreatic and extrapancreatic enzymes also participate in macronutrient digestion (24). The importance of the functions of the exocrine pancreas is reflected in the harmful malabsorption which ensues in patients with untreated pancreatic exocrine insufficiency, which is a characteristic consequence of chronic pancreatitis. The majority of chronic pancreatitis patients are diagnosed with exocrine insufficiency, and are treated using synthetic pancreatic enzymes which aim to provide restoration of digestive function.

1.3.2. Stimulation of exocrine function

The exocrine pancreas acinar and ductal cells must interact closely to coordinate to the release of pancreatic juice. The primary secretagogues for acinar enzyme secretion are acetylcholine (ACh) released from vagal neurons and cholecystokinin (CCK) released from endocrine cells (22). The most important ion in terms of ductal secretion is bicarbonate (HCO_3), which is essential for normal digestion. The high bicarbonate concentration produces an alkaline pH which protects the enzymes from acidic denaturation and increases the hydrolytic activity of the pancreatic enzymes in the intestinal lumen (24). The zymogen granules which store digestive enzymes are released by neurohormonal exocytosis with a meal, in which the secretory granule is moved to the apical surface (19). The enzymes from the pancreas digest starch (amylase), fats (lipase), and protein (trypsin) and other proteolytic enzymes (25). The enzymes amylase and lipase are secreted in an active form but conversely proteases are delivered into the duodenum in an inactive zymogenic form which requires activation. These include trypsin, elastase, chymotrypsin, carboxypeptidase and phospholipase A.

1.3.3. Proteolytic enzymes

All proteases are secreted as inactive precursors and the pancreatic juice entering the duodenum usually has no proteolytic activity. Trypsinogen is the inactive precursor for trypsin, which becomes activated by enterokinase secreted by the duodenal brush border, and is the key enzyme for the activation of all proteolytic enzymes in the duodenum (17). Trypsin has an autocatalytic effect, and cleaves and activates all other zymogens in a cascade effect (Figure 1.3).

1.3.3.1. Pancreatic lipolytic enzymes

Lipases from gastric and salivary glands play a minor role in the digestion of trygliceride and cannot fully compensate for insufficient pancreatic fat digestion, as pancreatic lipase is of paramount importance for fat digestion (17). Pancreatic lipase is secreted in its active form by acinar cells and hydrolyses two ester bonds of each triglyceride leading to the formation of free fatty acids and mononglyceride, the latter is absorbed in the small intestine (17)

1.3.3.2. Alpha-amylase

Pancreatic alpha (α)-amylase is the only carbohydrate-digestion enzyme which is produced in the pancreas and hydrolyses glycosidic bonds to free short chain polysaccharides. Alpha amylase digests starch where it is converted to short maltose, maltotriose and α-dextrins which are further digested by brush border enterocytes producing three sugars that can be absorbed (17).

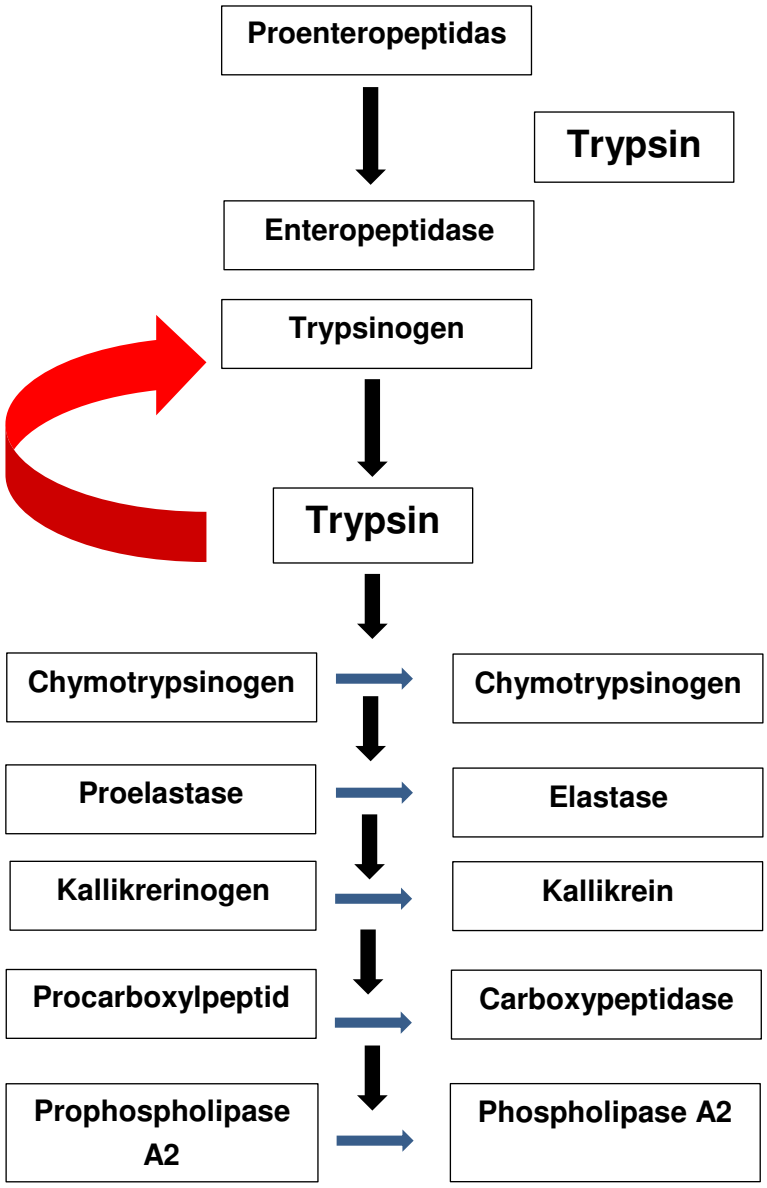

Figure 1.3: Pancreatic zymogen activation cascade

It is unknown what activates proenteropeptidase. Autoactivation of trypsinogen is relatively slow (red arrow) compared to the activation of trypsinogen by enteropeptidase. (Adapted from (26))

1.3.4. Pancreatic secretory patterns

Exocrine pancreatic secretion takes place in an interdigestive or postprandial pattern and in between there may be short cephalic or luminal stimulated phase of secretion. During phase 1, exocrine and gastric secretion is minimal, no bile enters the duodenum

and no gastric or upper small intestinal motor activity is detectable. If submaximal cephalic stimulus is delivered, or a meal is eaten, and during phase 1, enzyme secretion may be delayed (27). Interruption of the interdigestive phase continues as long as there is food in the stomach. GI motor activity begins and secretion increases during phase 2. As motor activity intensifies pancreatic secretions fluctuate with motor activity until secretion reaches peak rates. Phase 3 consists of a continued decrease in secretions, which is continued throughout phase 4 which represents a period of quiet until the interdigestive phase 1 resumes. The healthy pancreas adapts its exocrine secretions to nutrient ingestion, with a several fold increase in exocrine secretions occurring with nutrient ingestion compared to a fasting state.

Pancreatic secretions similar to gastric secretion are regulated by neural and hormonal mechanisms and are described to occur as follows;

- *During gastric and cephalic phases of gastric digestion, parasympathetic impulses are transmitted along the vagus nerves to the pancreas*
- *These parasympathetic nerve impulses stimulate increased secretion of pancreatic enzymes*
- *Acidic chyme containing partially digested fats and proteins enter the small intestine*
- *In response to fatty acids and amino acids, enteroendocrine cells in the small intestine secrete CCK into the blood. In response to acidic chyme, other enteroendocrine cells in the small intestinal mucosa liberate secretin into the blood*
- *Secretin stimulates the flow of bicarbonate-rich pancreatic juice*
- *CCK stimulates a pancreatic secretion that is rich in digestible enzymes*

Table 1.1: Neural and hormonal regulation of pancreatic secretions

***Summary of Tortora and Grabowski text describing neural and hormone regulation of pancreatic secretions (2000) (16)**

1.3.5. Pancreatic secretion during fasting

Secretory phases are associated with upper GI motility, bile entry to the duodenum and gastric secretion. In the fasting state, pancreatic enzyme secretion parallels cyclical changes in interdigestive intestinal motor activity during the daytime, with minimal enzyme output during phase 1, with maximal enzyme secretion immediately before the onset of or during phase 3 motility (27).

1.3.6. Postprandial secretion

Within a few minutes of ingestion of a meal, the interdigestive pattern is disrupted and postprandial secretion is induced, characterised by rapid increases in enzyme secretion reaching maximal values within the first post prandial hour, or even within 20-30 minutes (27). Following peak secretion, output stabilises and decreases postprandially until it reaches the end of the digestive period and resumes. The most important stimulus for postprandial enzyme response is duodenal nutrient exposure, and enzyme output is not solely regulated by the caloric content of a meal, but also by acute and chronic alterations in nutrient composition (27).

1.4. Endocrine pancreas

The endocrine pancreas consists of the islet of Langerhans; hormone-producing cells that are diffusely distributed in the parenchyma and do not connect directly to the pancreatic duct system. The islets are composed of spherical or ellipsoid clusters of cells which are embedded in endocrine tissue, and islet innervation is almost exclusively from the parasympathetic system (20). These islets consist of at least four different types, which are distinguished by different cytoplasmic secretory granules. Beta cells (β-cells) account for approximately 70% of islet cells producing the anabolic hormone insulin in conjunction with counteracting insulin-amyloid polypeptide A (IAPP)

(17). Insulin lowers glucose plasma levels and secretion is stimulated by glucose, amino acids, fatty acids, glycogen, glucogon-like peptide-1 (GLP-1) and cholecystokinin (17). Insulin release is stimulated by cholinergic and beta sympathetic fibres, and is required for the 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 (17, 28). Alpha cells (α-cells) account for 10% of islet cells and produce glucagon which increases glucose plasma levels stimulated by low levels and amino acids. Delta cells (δ-cells) secrete somatostatin which inhibits all GI hormones including insulin and glucagon. In contrast to this, glucagon release is inhibited by glucose, somatostatin and insulin. Pancreatic polypeptide is secreted by PP cells and is a hormone that inhibits pancreatic exocrine secretions, insulin secretion, bile secretion, and gallbladder contraction (17). Although islet cells account for far less pancreatic tissue than acinar cells, they are well perfused enabling rapid and effective release into systemic circulation.

1.5. Acute pancreatitis

The Atlanta Symposium devised 'The Atlanta Classification' (29) for the diagnosis of acute pancreatitis in 1992, which attempted to offer global consensus and universally accepted classification for acute pancreatitis. At that time acute pancreatitis was defined as an acute inflammatory process of the pancreas that frequently involves peripancreatic tissue and/or remote organ systems. This criteria was further updated by consensus consortium in 2012 to provide better understanding of the pathophysiology, and to classify acute pancreatitis using easily identified clinical and radiological criteria which received widespread agreement (30). Acute pancreatitis is a protean disease capable of producing findings ranging from mild pancreatic oedema to total organ necrosis, and from regional retroperitoneal inflammation to systemic multi-organ failure (31). The clinical course of an acute pancreatitis attack varies from a short period of

hospitalisation requiring supportive care, to prolonged hospitalisation requiring intensive care unit admission for the management of multiorgan failure, systematic inflammatory response syndrome (SIRS) and sepsis.

1.5.1. Presentation of acute pancreatitis

Depending on the severity of underlying pathological processes, acute pancreatitis may present anywhere on the spectrum of clinical severity from mild abdominal discomfort to catastrophic systemic illness (31). Acute pancreatitis is defined as an acute inflammatory process of the pancreas, with variable involvement of other regional tissues or remote organ systems (31).

1.5.2. Diagnosis of acute pancreatitis

Acute pancreatitis is diagnosed by using a combination of equivocal findings and at least two of the following criteria; severe abdominal pain characteristic of acute pancreatitis; blood serum amylase and/or lipase at least 3 times above the upper limit of normal; and/or findings indicative of acute pancreatitis on abdominal CT scan (30). While CT scans may be useful for diagnosis of acute pancreatitis, in identifying risk factors and disease complications, it is generally not required to make the diagnosis and may be delayed (32, 33). Acute pancreatitis can be subdivided into two types; interstitial oedematous pancreatitis and necrotising pancreatitis (30). Interstitial oedematous pancreatitis is characterised by diffuse or localised enlargement of the pancreas due to inflammatory oedema (30). There may be some peripancreatic fluid and clinical symptoms usually resolve within the first week (34). Necrotising pancreatitis most commonly manifests as necrosis involving both the pancreas and peripancreatic tissues, less commonly as necrosis of only the pancreatic parenchyma tissue, and rarely as the pancreatic parenchyma alone (30). About 5-10% of patients

develop necrosis of the pancreatic parenchyma which is associated with increased requirement for intervention and mortality (30).

1.5.3. Determination of disease severity

Acute pancreatitis is known to be an evolving and dynamic disease, and the severity may escalate during the course of the disease. The Atlanta criterion for severity includes organ failure, particularly acute lung injury, (presented clinically as acute respiratory distress syndrome (ARDS)), renal failure and shock. Local complications may include abscess, necrosis and pseudocyst. In terms of disease severity, acute pancreatitis may be stratified into three groups; mild acute pancreatitis, moderate-severe acute pancreatitis, and severe acute pancreatitis (30). Mild acute pancreatitis is characterised by disease in the absence of organ failure and local or systemic complications, discharge is usually early and mortality is very rare (30). Moderate to severe acute pancreatitis includes the presence of transient organ failure or local or systemic complications in the absence of persistent organ failure (30). Severe acute pancreatitis is a condition characterised by persistent single or multiple organ failure. It is characterised by organ failure that develops during the early phase as a result of activation of the cytokine cascade resulting in SIRS (30). There is a considerable risk associated with the development of multi organ failure or SIRS in the first few days of disease, with accompanying mortality rates ranging from 36%-50% (30). The coupling of infected necrosis of the pancreas in patients with persistent organ failure is thought to be associated with extremely high mortality rates (35, 36).

1.5.4. Aetiology

The predominant causes of acute pancreatitis are alcohol intake or gallstones which may cause frequent inflammation. Together, these two causes are thought to be

responsible for approximately 80% of cases. Excessive alcohol consumption is believed to be responsible for 30-35% of all cases (37). Biliary tract disease is attributable to 40-45% of cases, 10-15% are associated with less frequent causes such as hyperlipidaemia and drug abuse, while 10% of all cases are considered idiopathic (37).

1.5.5. Epidemiology

The incidence of acute pancreatitis worldwide is thought to range from 13 to 45 per 100,000 (38-40). In the UK, age-standardised admission rates for acute pancreatitis increased from 14.5 per 100,000 in 1989/1990 to 20.7 per 100,000 in 1999/2000 (41). This mirrors earlier reports in neighbouring Scotland, where the crude admission rate for acute pancreatitis rose from 25.8 per 100,000 in 1985 to 41.9 per 100,000 in 1995 (42). The incidence worldwide is also thought to be rising and this is most likely attributable to increasing alcohol-related pancreatitis. In Ireland, hospital admissions for acute pancreatitis increased from 17.5 per 100,000 in 1997 to 23.6 per 100,000 in 2006, reflecting a 54.1% rise (43). This finding was also coupled with a marked increase in alcohol-associated admissions compared to biliary tract disease, and this rise was more pronounced in the younger age groups (43). In Ireland the increasing trend in alcohol-related acute pancreatitis parallels the rises seen in *per-capita* alcohol consumption, where there has also been a prominent increase in binge-drinking amongst young people. Of particular importance was the publication of an EU-wide study which reported a positive correlation between pancreatitis death rates and per capita alcohol consumption in 14 Western countries, with the magnitude of association mostly consistent across many jurisdictions (44). Unfortunately, Ireland was not included in this study, and therefore it was not possible to extract data. The incidence of first-attack acute pancreatitis in England is relatively low at 10 per 100,000, higher in the Netherlands, Germany and Norway (16-20 per 100,000), and considerably higher

in other Scandinavian countries such as Sweden and Finland (45). First-attack acute pancreatitis is defined as acute pancreatitis without hospital visit with this diagnosis during minimum one year preceding index visit (46). The incidence of first attack acute pancreatitis in the US is the highest at 32-44 per 100,000, and the reasons for this are unclear (45). Differences in geographical variations of acute pancreatitis are incompletely understood and might be reflective of variances in risk factor prevalence in different countries. It may be due to individual differences in genetic susceptibility to suffer an attack of acute pancreatitis, and the role of genetic factors in this process is thought to be increasingly important (47). Other factors that may be attributable to confounding reports of incidence may be disparities in the use of classification criteria, and the validity and accuracy of data sources used in studies.

1.5.6. The pathogenesis of acute pancreatitis

As described in section 1.2.1, the pancreas has three basic functions, which include secretion of sodium bicarbonate to neutralise hydrochloric acid from the stomach, secretion of digestive enzymes, and secretion of hormones to regulate intermediate metabolism postprandially. Digestive enzymes (with the exception of lipase and amylase), are synthesised and secreted in an inactive proenzyme form to protect against pancreatic auto digestion. Two major independent early cellular events implicated in the pathogenesis of acute pancreatitis are intra-pancreatic trypsinogen activation and nuclear factor kappa-light-chain-enhancer of B activated cells (NF-kB) activation (48) (Figure 1.4 and 1.5). NF-kB is a protein complex that controls the transcription of DNA, cytokine production and cell survival and plays a key role in regulating immune response to infection, where incorrect regulation has been linked to cancer and inflammatory diseases, amongst others (48). Premature intra-pancreatic trypsinogen activation to trypsin causes an activation cascade (Figure 1.3) with

additional trypsinogen and other digestive proenzymes actively converted to active enzymes causing pancreatic digestion and inflammation.

A number of protective mechanisms work together to protect against premature activation of trypsinogen and other prodigestive enzymes. A peptide specific acute phase protein known as serine protease inhibitor kazal type-1 (*SPINK1*) has the capacity to inhibit trypsinogen if it is activated within the acinar cell, however; trypsinogen greatly outnumbers *SPINK1* molecules, and capacity is limited if more trypsinogen than *SPINK1* is released (49). Gain-of-function genetic trypsin mutations or loss-of-function mutations in trypsin inhibitors increase the risk of acute pancreatitis (50, 51).

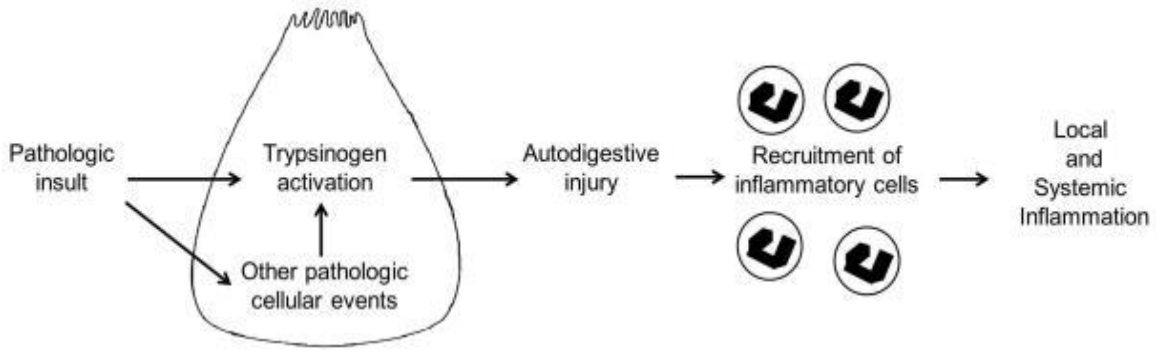

Figure 1.4: The trypsin-centred theory of pancreatitis

Intra-acinar trypsinogen activation is the central event in this theory and is responsible for local injury and systemic inflammation. Other pathologic events like endoplasmic reticulum stress, autophagy, lysosomal dysfunction, pH alterations, oxidative stress, and bile duct dysfunction, are linked to the central event (trypsinogen activation) in this theory.

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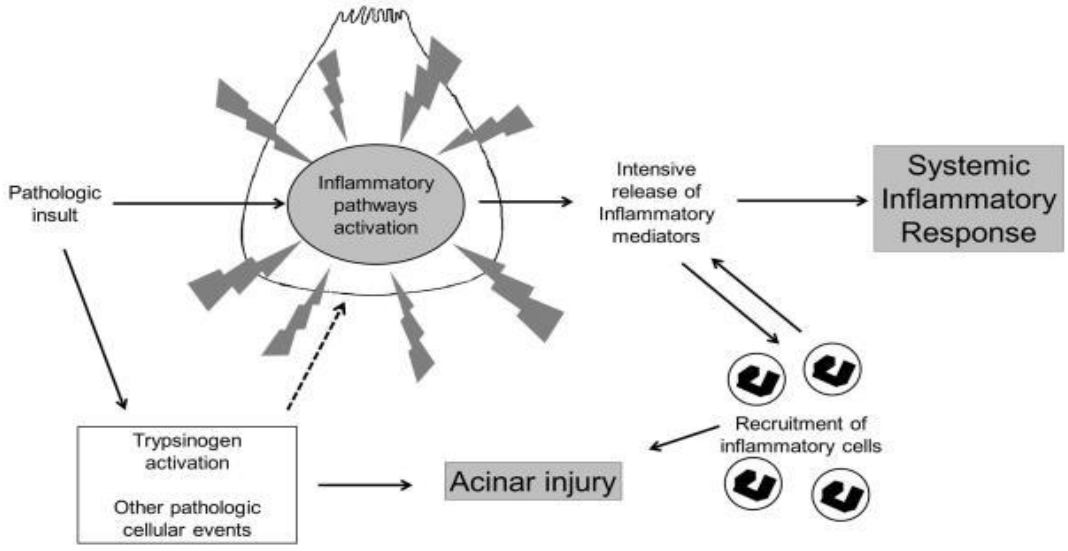

Figure 1.5: Pathogenesis of acute pancreatitis

Activation of inflammatory pathways (such as NF-kB – (nuclear-factor kappa-light-chain-enhancer of B activated cells)) in the acinar cell leads to intense inflammatory response causing local and systemic inflammatory response to acute pancreatitis

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1.5.7. Treatment of acute pancreatitis

Acute pancreatitis is known to have a highly variable clinical presentation, fluctuating between mild and moderate cases, to a severe systemic inflammatory pancreatic process leading to necrosis, multi-organ failure and death (52). Patients should be carefully assessed for potential signs of systemic inflammation and organ dysfunction, and supportive measures should be initiated, which represents the current standard of care. Patients with gallstone-related acute pancreatitis may undergo endoscopic retrograde cholangiopancreatography and sphincterotomy (53). Due to the absence of effective pharmacological treatments the management of acute pancreatitis remains supportive (54).

1.5.8. Complications

The problems which occur as a result of acute pancreatitis may be subdivided into local or systemic complications. Local complications include; pancreatic necrosis, acute pancreatic fluid collection (APFC), acute pancreatic pseudocyst, walled off necrosis, and acute necrotic collection. Other extrapancreatic local complications include gastric outlet dysfunction, splenic or portal vein thrombosis, and colonic necrosis (30). Systemic complications include ARDS, SIRS, sepsis, and renal or hepatic failure. According to the Atlanta symposium, exacerbations of pre-existing co-morbidities, such as coronary artery disease or chronic lung disease (precipitated by the presence of acute pancreatitis) are defined as systemic complications (30).

1.6. Recurrent acute pancreatitis

Recurrent acute pancreatitis is defined as more than one well documented and separate attacks of acute pancreatitis (requiring hospitalisation) that almost or completely resolves, with more than 3 months between attacks (55-57). Recurrent acute pancreatitis is an enigmatic process as complications of acute pancreatitis, such as pseudocyst, fluid collection and oedema, may persist after normalisation of pancreatic enzymes and patient symptoms. However, demonstrating that the pancreas is normal between attacks of pancreatitis without any evidence of chronic pancreatitis is extremely difficult in clinical practice. It is difficult to diagnose chronic pancreatitis at an early stage, before the occurrence of irreversible morphological change and permanent loss of endocrine and exocrine function. Therefore it is difficult to differentiate between patients with recurring episodes of acute attacks of pancreatitis, *versus* early stage chronic pancreatitis. Historically, it was thought that after an initial attack at least 30% of patients will experience recurrence (55). However, few

population-based epidemiological studies exist worldwide outlining the prevalence of recurrent acute pancreatitis. One large study including over a thousand patients from five European countries found a 27% recurrence rate with alcohol the primary aetiology, and 25% recurrence rate of gallstone related aetiology (58) The most common causes of recurrence are thought to be alcohol consumption, common bile duct obstruction, Sphincter of Oddi dysfunction, ductal abnormalities or obstruction, and genetic mutations (59).

Minor pancreas injury can lead to large local and often systemic inflammation. Some patients experience only mild inflammation, whilst others endure severe systemic engrossment which may lead to organ failure and mortality. The reasons for this interpatient variability are unknown. Patients with acute pancreatitis usually respond to treatment, however symptoms may recur. Repeated episodes of acute pancreatitis have the potential to develop into recurrent acute pancreatitis and further to chronic pancreatitis. Acute pancreatitis is characterised by an acute inflammatory response, and chronic pancreatitis which is ongoing inflammatory injury. Destruction of acinar cells takes place, by whatever cause, leading to the activation of several inflammatory cells such as macrophages and granulocytes, which secrete pro-inflammatory cytokines. Pro-inflammatory cytokines in turn release pancreatic stellate cells known play a central role in initiating and promoting inflammation and specifically the development of fibrosis, which is known to be a major risk factor for pancreatic cancer. Exocrine and endocrine insufficiency may be present in patients following recovery from a single episode of acute pancreatitis, even up to five years later (60). Therefore, it may be assumed that patients with recurrent attacks of acute pancreatitis have similar functional deficits after seemingly recovering. The major risk for development of pancreatitis results from the premature activation of trypsin, followed by zymogen

activation, tissue auto-digestion and the generation of a robust immune response and its sequelae (61).

1.7. Chronic pancreatitis

1.7.1. Chronic pancreatitis overview

The Cambridge definition of chronic pancreatitis is a chronic inflammatory disease of the pancreas characterised by irreversible morphological change typically causing pain and/or permanent loss of function (62). Loss and destruction of acinar and islet cells of the pancreas and ongoing inflammatory processes lead to the development of fibrosis. Progressive loss of exocrine function results in maldigestion, malnutrition, weight loss, loss of muscle mass, bone health issues, micronutrient deficiencies and reduced functional capacity. The loss of pancreatic endocrine function eventually leads to diabetes and related complications.

1.7.2. Diagnosis

Chronic pancreatitis is frequently diagnosed based on imaging studies and pancreatic function testing and diagnostic criteria relies on histological evidence of irreversible damage to the pancreas in the setting of ongoing inflammation which remains the most definitive diagnosis (63, 64). This diagnosis of chronic pancreatitis relies on identification of the permanent and irreversible destruction of pancreas and is grounded in the disease morphology. Reliance on this definition is restrictive and limits the possibility of early diagnosis before the appearance of morphological changes, which signify the pancreas has undergone irreversible destruction. In 2016, a new draft consensus definition was agreed to encompass new developments and advancements in genetics, epidemiology, molecular biology and modelling, providing insights into the

pathogenesis of the disease (65). This new mechanistic definition describes chronic pancreatitis as ‘a pathogenic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress’ (65). Chronic pancreatitis is complex in nature and this definition separates risk factors from disease activity markers, and endpoints, allowing for rational approach to early diagnosis, classification and prognosis (65). Knowledge of the aetiological pathway using genetic and environmental data will target the underlying cause, allowing a more personalised approach, rather than treating symptoms common to all aetiologies (66). Whilst this definition has reached initial acceptance, debates must take place to achieve international agreement. Efforts in chronic pancreatitis are now aimed at gleaning early knowledge of the basis of risk that could be used to target therapy and change the diseases from treating end-stage symptoms and complications to preventing the disease.

1.7.3. Pathology

The pathology of chronic pancreatitis is described as progressive exocrine tissue destruction with replacement of normal pancreatic tissue with fibrosed tissue leading to gland hardening, enlargement and atrophy. The morphological classification of chronic pancreatitis entails irregular sclerosis with destruction and permanent loss of exocrine parenchyma which may be focal, segmental or diffuse (67). Those changes may also be associated with varying degrees of duct dilation.

The pathogenesis of chronic pancreatitis has been hypothesised in a number of ways. The necrosis-fibrosis hypothesis suggests that acute pancreatitis, probably in its severe relapsing form, causes chronic pancreatitis (68). It is postulated that an acute inflammation leads to periductal injury and fibrosis that finally compresses the ductal

lumen (69). This obstruction causes acinar cell atrophy and calculi precipitation due to stasis and further fibrotic tissue formation (70) (Figure 1.4). The sentinel acute pancreatitis event (SAPE) hypothesis encompasses elements of a number of different hypotheses including; the toxic-metabolic hypothesis, the oxidative stress and the necrosis hypothesis. The SAPE hypothesis suggests that an initial 'sentinel' event of acute pancreatitis occurs which has sufficient severity to initiate an inflammatory process (Figure 1.8). This causes pancreatic parenchymal infiltration by macrophages, activation of stellate cells, and the recruitment of lymphocytes and monocytes into the pancreas which represents an early pro-inflammatory stage. Previously opinion favoured the necrosis-fibrosis hypothesis describing chronic pancreatitis as an initial acute process progressing to chronic irreversible damage resulting from repeated attacks. However, despite its value in understanding the disease pathogenesis, this concept fails to clarify why patients with little or no evidential necrosis can advance to chronic pancreatitis.

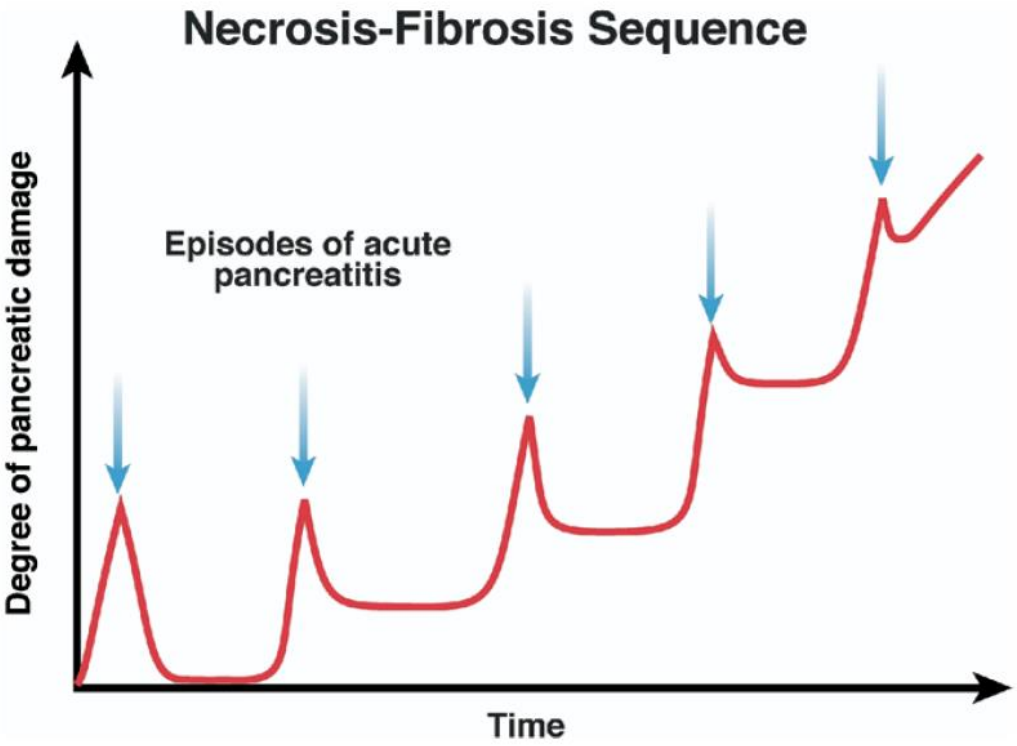

Figure 1.6: The necrosis-fibrosis hypothesis of pancreatic injury

This diagram suggests that cumulative pancreatic damage occurs with recurrent episodes of acute pancreatitis.

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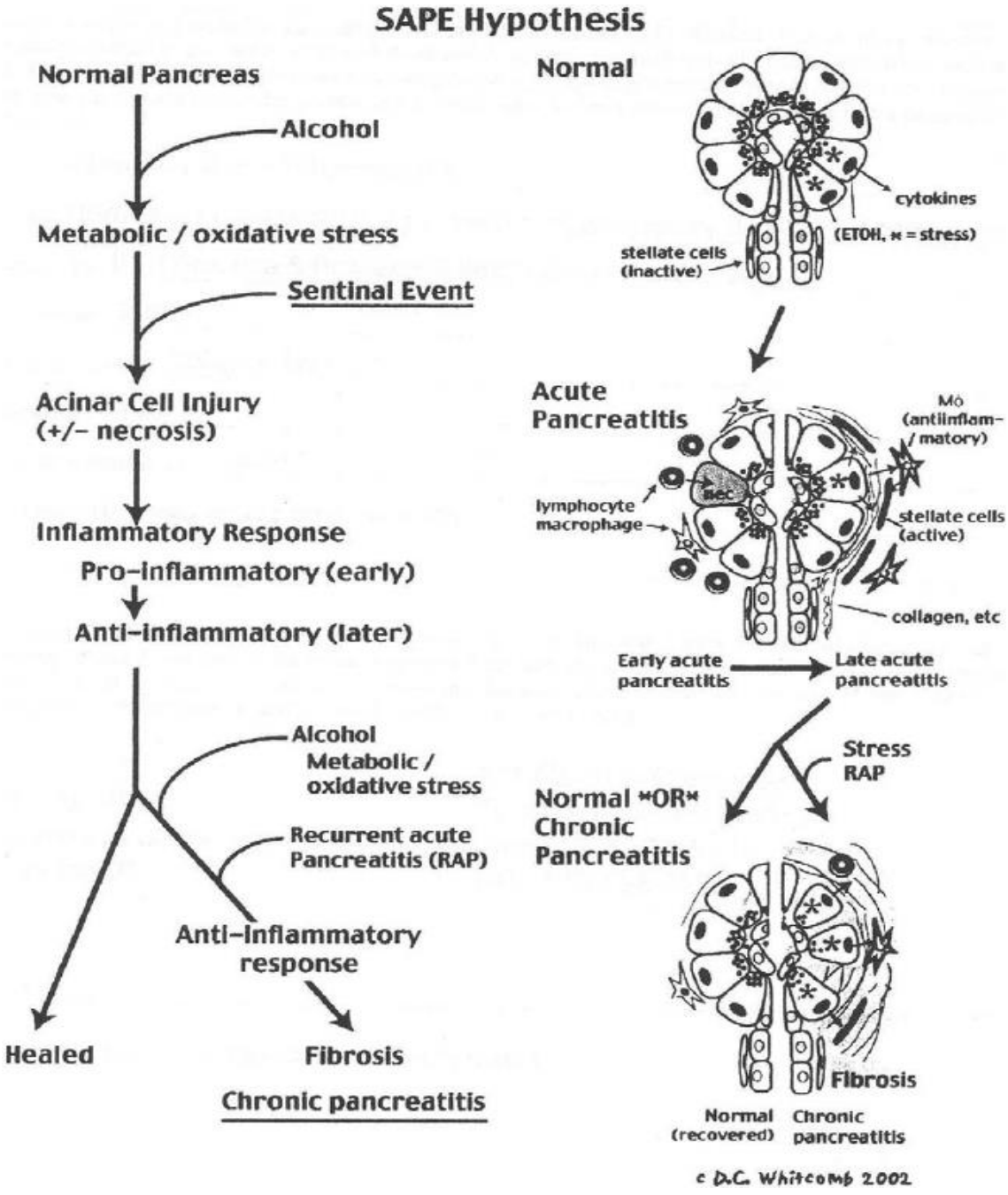

Figure 1.7: The SAPE hypothesis of pancreatic injury

The diagram explains the 'sentinel' episode of acute pancreatitis which is necessary to initiate anti-inflammatory and pro-fibrogenic cells

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1.7.4. Classification of chronic pancreatitis

Key publications have suggested that the ideal chronic pancreatitis classification system would be simple, objective, accurate, relatively non-invasive, incorporating aetiology, pathogenesis, structure, function and clinical status into one overall schema (63, 73, 74). Several classification systems for chronic pancreatitis have been proposed in recent years; however pancreatologists have struggled to reach a comprehensive and manageable classification system. The most widely cited is the Marseille classification system and its revisions (75, 76), which is invaluable in clinical practice, however this proves to be more useful in defining chronic pancreatitis than serving as a classification system. The Cambridge classification (77), though 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 (63). Therefore the Cambridge classification serves more as a staging system once the diagnosis is made rather than a system for classifying chronic pancreatitis aetiology. A number of other systems have been proposed including a clinically based classification system for alcohol chronic pancreatitis (78), and a clinical aetiology system for chronic calcifying pancreatitis, and remain to be widely accepted. The Manchester classification (79) categorises clinically distinct stages which are relevant to patient management and identifies 3 stages of disease; mild, moderate, and end-stage, each containing characteristic criteria. This system is practical, feasible and applicable to clinical practice however it has not been prospectively evaluated.

A further revision of the Cambridge classification has been proposed, and this system (M-ANNHEIM) is based on multiple risk factors and interactions on the course of disease (80). This system is simple, objective, accurate, non-invasive and encompasses aetiology, different disease stage, and degrees of severity. A further classification, the TIGAR-O system (63) incorporates new insights of various risk

factors including; toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis or obstructive, and is widely used and clinically relevant.

1.7.5. Disease presentation

The predominant presenting symptom in most, but not all patients is abdominal epigastric pain, which is described as dull, constant, or intractable in nature. This pain is usually located in the upper right quadrant of the abdomen, or central abdomen, radiating posteriorly to the back or laterally to the right or left flank. It may be stimulated by oral intake, and associated with nausea, and vomiting, and is relieved by sitting forward (81). In other patients there may be no pain and clinical presentation is characterised by exocrine or endocrine symptomology, including steatorrhoea, weight loss or diabetes mellitus. Other less common presentations include biliary obstruction with recurrent episodes of mild jaundice, cholangitis or vague attacks of indigestion (28). Obstruction of the splenic vein by the inflamed tail of the pancreas can result in left-sided portal hypertension, gastric varices and GI bleeding. Chronic pancreatitis is similar in presentation to pancreatic cancer, and distinguishing between the two entities may be troublesome (82).

1.7.6. Disease progression

Disease progression often begins with an initial early phase characterised by episodes of abdominal pain that can be mistaken for acute pancreatitis, as clear-cut evidence of chronic pancreatitis can be absent at that time (64). Although chronic pancreatitis is thought to require an initial episode of acute pancreatitis, some patients with acute pancreatitis of varying aetiologies do not progress to chronic pancreatitis (83). Disease progression is heavily associated with continued smoking, alcohol intake and genetic susceptibility to risk (64, 84). The presentation, clinical course and natural history of chronic pancreatitis are extremely variable, and individual patients experience vastly

different symptomology and disease presentation. There are a number of stages thought to be present in chronic pancreatitis. Initially there is a pre-clinical stage which may be characterised by some non-specific symptoms or the absence of symptoms. This is followed by a stage of recurring attacks of acute pancreatitis but lacking morphological changes as evidence for the diagnosis of chronic pancreatitis. In the next stage pain may be intermittent or constant, there are morphological signs of chronic pancreatitis, and exocrine insufficiency becomes apparent. Finally, in the latter stages, acute pain symptoms may have elapsed, and exocrine and endocrine insufficiency are known to be common.

1.7.7. Aetiology

1.7.7.1. Alcohol

Alcohol has long since been considered the predominant aetiology of chronic pancreatitis worldwide, with approximately 80% of cases being attributed to excess alcohol consumption (45). The risk of alcohol-induced pancreatitis increases logarithmically with cumulative alcohol use, but there is thought to be no scientifically justifiable threshold (85). By convention it is assumed that 50-80g of alcohol per day (less in females) for 6-12 years is required to produce symptomatic pancreatitis and the disease risk increases with amount and duration of consumption (86-88). There is also thought to be individual variability with some people developing chronic pancreatitis with as low as 20g of alcohol per day, and others may consume >200g per day before disease develops (89, 90). In fact little is known about individual susceptibility and sensitivity to alcohol-related pancreatic damage. However, is it is widely known that only a minority of heavy drinkers develop clinically evident pancreatitis (91-93). The risk of chronic pancreatitis in those who smoke cigarettes and drink alcohol is 8-fold higher than the general population (94). However approximately only 3-15% of heavy drinkers

will develop chronic pancreatitis (85, 95), suggesting that other risk factors play an important role. It is unclear why some alcohol dependents develop pancreatitis, while others do not, and liver cirrhosis is more commonly believed to be pathological of heavy drinking. One study showed that in patients with early onset of chronic pancreatitis (before 35 years of age), alcohol intake of less than 50g per day induced earlier disease (characterised by more frequent severe pain, calcifications and complications) compared to adult chronic pancreatitis patients without alcohol use (96). Therefore, alcohol may cause chronic pancreatitis (in some susceptible patients), but importantly, relatively small amounts may also accelerate disease onset and deterioration in predisposed patients (85). Importantly, smoking, genetic predisposition and environmental factors appear to play an essential role in disease pathogenesis in all patients. A combination of genetic, environmental and metabolic factors contribute to the development and recurrence of acute pancreatitis and chronic pancreatitis (66).

1.7.7.2. Smoking

Smoking is an independent aetiological risk factor for the development of chronic pancreatitis (86). Smoking is also known to accelerate disease progression and patient's perception of pain (97). Because of the close correlation between tobacco smoking and alcohol intake, it is difficult to quantify the pathogenic roles of the two factors in patients who smoke and drink alcohol. However, studies have shown that the prevalence of smoking is higher in non-alcoholic idiopathic chronic pancreatitis patients than the general population, and is associated with disease progression, including calcifications and diabetes in patients over 35 years at disease onset (98, 99). Most importantly, even in patients who report complete alcohol abstinence, smoking remains a significant risk factor (98).

1.7.7.3. Idiopathic aetiology

In a substantial number of patients, the aetiology of the disease remains obscure, and 10-25% of patients are classified as having idiopathic chronic pancreatitis (85). Idiopathic chronic pancreatitis is diagnosed by the exclusion of all other potential causes, including rare ones and has been shown to comprise two clinically distinct entities; namely early-onset and late-onset disease (85).

(1) Early-onset idiopathic chronic pancreatitis is characterised by symptoms occurring during the first two or three decades of life, typically defined as disease occurring before 35 years of age (100). Patients usually have a long course of substantial pain and develop morphological and functional damage more slowly and less frequently than patients with alcohol or nicotine related disease

(2) Late-onset pancreatitis consists of the development of clinical symptoms typically after 35 years of age (100), which most often occur after the fifth decade of life. These patients typically have milder, or an eventually painless clinical course, with exocrine or endocrine insufficiency as first symptoms.

Both forms of idiopathic chronic pancreatitis differ from alcoholic pancreatitis in their equal gender distributions and much slower rate of calcification (100)

1.7.7.4. Genetic

Once formerly assumed to be a self-inflicted disease resulting from excessive alcohol consumption, chronic pancreatitis is now recognised as a complex inflammatory disease which has a distinct genetic predisposition (101). Pancreatitis is thought to rarely be caused by a single factor and the majority of patients with acute, recurrent acute and chronic pancreatitis are thought to have multiple variants in a gene, or epistatic interactions between multiple genes coupled with environmental stressors (50). In 1996 a breakthrough in the understanding of recurrent acute pancreatitis and

chronic pancreatitis came with the discovery of gain-of-function mutations in the gene encoding cationic trypsinogen (known as *PRSS1*) that causes hereditary pancreatitis (51). Recurrent acute pancreatitis and chronic pancreatitis have been associated with loss-of-function mutations that encode serine protease inhibitor Kazal type-1 (*SPINK1*) (102) and cystic fibrosis transmembrane conductance regulator gene (*CFTR*) (103, 104). Mutations in *CTRC* (105, 106) and calcium-sensing receptor gene (*CASR*) are also associated with smaller increases in risk (101).

Chronic pancreatitis is most often linked to mutations involving the exocrine pancreas. Molecular genetic studies provide critical information that highlights trypsin as the central molecule in initiating acute pancreatitis, and susceptibility to this disease appears to be related to the body's ability to protect itself from trypsin activation (49). The major risk factor for the development of acute and chronic pancreatitis lies in the risk of premature trypsin activation, followed by zymogen activation, tissue autodigestion, followed by a vigorous inflammatory sequelae (61). Regulation of trypsin in the acinar cell is dependent on regulation of intracellular calcium concentrations (107). The effect of genetic variations cannot be understood in isolation and must be considered in the context of environmental, metabolic, and other genetic factors that influence disease activity (101). Understanding the contribution of genetic factors to pancreatitis risk and disease pathogenesis could, in the future, lead to early aetiology-based treatments.

1.7.7.5. Other causes

Other less common causes account for approximately >10% of all cases of chronic pancreatitis. Such causes include hyperparathyroidism, hypertriglyceridemia, pancreatic duct obstruction, trauma, pancreas *divisum*, cystic fibrosis, autoimmunity and hereditary reasons (45). Pancreas *divisum* is an abnormality occurring when the dorsal and ventral anlage fail to fuse during the 6^{th} to 8^{th} week of gestation (108).

Pancreas *divisum* is characterised not only by anatomical morphology but also by the physiology in which the majority of pancreatic juice drains to the duodenum *via* the duct of Santorini, and a minority of pancreatic juice drains *via* the duct of Wirsung to the duodenum (109). Although the clinical significance of pancreas *divisum* remains controversial, it has been associated with chronic abdominal pain and recurrent acute pancreatitis (108). Pancreas *divisum* has not been shown to be a cause of pancreatitis, but instead associated with the development of chronic pancreatitis when coupled with other genetic and environmental causes. One study found that the pancreas *divisum* was present in 7% of subjects without pancreatitis, 7% of subjects with alcohol-induced pancreatitis and in 47% of *PRSS1*-, *SPINK1*-, and *CFTR*-associated genetic pancreatitis (110). This study suggests that the occurrence of pancreas *divisum* is not different between patients and controls however; it was higher in patients with a genetic disposition highlighting the cumulative effect of these cofactors in the development of pancreatitis.

1.7.8. Epidemiology of chronic pancreatitis

The epidemiology of chronic pancreatitis worldwide has not been investigated thoroughly, the number of population based studies is scarce and there are no reports available from many countries worldwide. Reports for chronic pancreatitis are much less frequent than for acute pancreatitis, possibly due to acute pancreatitis occurring more often and due to the associated mortality rates for acute pancreatitis, sparking greater clinical research and interest. Another explanation may be that the diagnosis of chronic pancreatitis, particularly in the early stages is more difficult to establish (45). Many of the early reports of chronic pancreatitis helped to describe the clinical profile and the natural course of the disease in often small select cohorts of patients. It must be considered that it may be inappropriate to compare epidemiological studies, especially if they were performed years apart, due to differences in disease diagnosis

and classification (45). Largescale nationwide studies of the population-based frequency of chronic pancreatitis, including aetiological considerations, are needed from many countries worldwide, to quantify the disease burden. In Ireland (43) and in Western countries the incidence of acute pancreatitis has increased and there have also been increases in hospital admissions for both acute and chronic pancreatitis (45). These upward time trends are likely to represent a change in the prevalence of the main aetiological factors including alcohol, gallstones and genetic susceptibility (45). The epidemiology of chronic pancreatitis worldwide will be discussed in depth in Chapters 2 and 7.

1.7.9. Treatment and management

There is no definitive treatment for chronic pancreatitis and the disease cannot be cured or reversed. Management of chronic pancreatitis is challenging and most patients remain symptomatic despite therapy (64). Once the correct diagnosis has been established, and the underlying aetiology deciphered, the aim of treatment is to minimise the effect of associated symptoms to enable patients to maintain as much function as possible. As chronic pancreatitis is irreversible, efforts should be focussed on preventing disease, which relies on knowledge of the underlying cause of risk and mechanisms of disease progression. The management principles of chronic pancreatitis are centred on the treatment of pain, management of endocrine and exocrine insufficiency, the treatment of nutrition-related consequences of disease, and management of associated multimorbidities. This includes introducing lifestyle changes and referral to addiction services where necessary.

Chapter 2 which follows describes the thesis context, rational and aims which underpin this work.

2. Chapter 2 – Thesis outline, rationale and aims

This chapter describes the background to the studies, and the body of work undertaken in this thesis along with the rationale underpinning each study.

2.1. Thesis context and rationale

While the understanding of chronic pancreatitis has improved in recent times, there are a number of areas where knowledge is lacking. Our research group focused heavily on the clinical and in particular the nutritional management of chronic pancreatitis in the last number of years (111-116). Arising from this work, and along with the research team, the thesis author identified four key areas of chronic pancreatitis management that warranted exploration.

1. Whilst several guideline documents have been published in recent years (117-123) on the management of patients with chronic pancreatitis, little is known regarding knowledge of, or adherence to guidelines among clinicians. Therefore the thesis author aimed to conduct a 2-part nationwide survey of chronic pancreatitis management in Ireland; of surgeons and gastroenterologists, and of general practitioners. Subsequently, it was apparent that there were many gaps in practice, most acutely, at community level. Therefore, this led to the development of evidence-based and collaborative chronic pancreatitis guidelines for general practitioners in Ireland (124).

2. It became apparent that the scale of chronic pancreatitis in Ireland needed to be measured and understood in order to effectively disseminate the groups prior findings, and in order to effect change in management. Therefore, the epidemiological aspect of this work evolved from the need to quantify chronic

pancreatitis in Ireland. In particular, the need to determine the prevalence of the disease, and to quantify hospital activity compared to internationally reported rates, was deemed critical. In fact, the prevalence of chronic pancreatitis is Ireland has never been quantified, and therefore the burden of this disease is unclear. Consequently, there are no data on population-based frequency of disease to highlight the need for healthcare service and budgetary consideration. Therefore, along with the research team, the thesis author sought to assess the burden of chronic pancreatitis in the Irish population, to compare the prevalence of the disease with different populations, and to examine trends in disease prevalence and aetiology over time.

3. As mentioned earlier, efforts by our research group were for many years focussed on addressing the considerable gaps in the evidence base, regarding the nutritional management of patients with chronic pancreatitis. While knowledge of the nutritional management of chronic pancreatitis has evolved considerably, there are key areas related to malabsorption which require attention. Many guidelines have been established which have focussed on the diagnosis and management of PEI, however little attention has been focussed on other factors affecting malabsorption in chronic pancreatitis, such as SIBO. Therefore, the thesis author sought to evaluate the prevalence of SIBO in chronic pancreatitis patients.

4. The genetic element of this work developed due to the need to evaluate the importance of genetic susceptibility and environmental risks in our pancreatitis patients. Many patients were attending our specialist clinics with apparently idiopathic aetiology chronic pancreatitis diagnoses, which had not undergone genetic analysis. Similarly, many patients with chronic pancreatitis were classified as having an alcohol-associated aetiology. However, in some cases

alcohol consumption histories were potentially inaccurate, or appeared to be inconsistent with the threshold amounts required to produce alcoholic pancreatitis. This led to the design of a study to explore genetic susceptibility in an Irish chronic pancreatitis patient population. The ethical considerations and implications for susceptibility genetic testing are discussed in detail in Chapter 8.

The broad objective of this body of work was to design studies which would generate output that had a strong clinical emphasis, as well as a focus on service improvement. The overarching aim was to enhance clinical management, and to improve clinical knowledge, thereby leading to innovations which would be directly applicable to practice, and would therefore improve the management and outcomes of patients with chronic pancreatitis. It was also envisaged that the results of the studies would lead to policy requirements and recommendations that could contribute to the development of programmes and frameworks for the management of chronic pancreatitis as a chronic disease in Ireland.

2.2. Thesis outline

In this thesis, four studies were undertaken to answer the research questions which are outlined in the thesis aims (Section 2.3). These core thesis chapters are numbered Chapters 5 to 8. Chapter 5 of this thesis describes a study investigating the management of chronic pancreatitis at both acute and community settings. This is followed by chapter 6, which describes an epidemiological study of chronic pancreatitis prevalence and hospital activity in Ireland. Chapter 7 describes a study on the prevalence of small intestinal bacterial overgrowth (SIBO) in patients with chronic pancreatitis with pancreatic exocrine insufficiency (PEI). Chapter 8 of this thesis, details

a study of major pancreatic gene mutations in idiopathic and alcohol-induced chronic pancreatitis patients.

Figure 2.1 details the thesis outline and evolution of these studies.

Figure 2.1: Outline of thesis studies

2.3. Overall thesis aims

Research question 1:
What is the current management of chronic pancreatitis in Ireland?

Objective 1

To survey specialists (gastroenterologists and consultant surgeons) about their current management of chronic pancreatitis in hospital-based care

Objective 2

To survey general practitioners (GPs) nationwide regarding their current practices in the management of chronic pancreatitis

Objective 3

To develop general practice guidelines for chronic pancreatitis

Research question 2:
What is the population-based prevalence of chronic pancreatitis in Ireland?

Objective 4

To investigate the prevalence of chronic pancreatitis using hospital discharge data from the Nationwide HIPE database

Objective 5

To explore the data for temporal changes in hospital discharges for chronic pancreatitis

Objective 6

To describe the aetiology of chronic pancreatitis in Ireland

Research question 3:
Do patients with chronic pancreatitis and pancreatic exocrine insufficiency have SIBO?

Objective 7

To estimate the presence of SIBO in a cohort of non-surgical chronic pancreatitis patients with mild and moderate PEI and compared with (age, sex and smoking-status) matched healthy controls

Research question 4:
Do Irish chronic pancreatitis patients have common major pancreatic gene mutations?

Objective 8

To analyse the presence of specific common gene variants in *SPINK1*, *PRSS1* and *CFTR* in patients with idiopathic and alcohol aetiology chronic pancreatitis compared with healthy controls

Chapter 3 focuses on the four key aspects of chronic pancreatitis which underpin this thesis. The literature review provides a background to the thesis research studies.

3. Chapter 3 – Chronic pancreatitis

3.1. Introduction

Chronic pancreatitis, like many chronic diseases, is associated with much personal suffering, excess morbidity, mortality and substantial use of healthcare resources (114). Knowledge of the aetiology and pathogenesis of chronic pancreatitis has greatly improved in the last 25-30 years. Previously the aetiology of chronic pancreatitis was oversimplified and attributed solely to excess alcohol intake, with the remainder of patients characterised as non-alcohol associated pathology. Over the past two decades genetic studies have made progress in defining the pathogenesis of chronic pancreatitis and it is now confirmed that genetic susceptibility plays a fundamental role in disease risk and development (50). Insights gained from studies of genetic variations and environmental factors have transformed current understanding of chronic pancreatitis. Research efforts are now focussed on decoding the meaning of gene variants for individual patients, and how to apply knowledge for effective treatment decisions. Advancements in the understanding of the etiopathogenesis of chronic pancreatitis have led to the recognition of the role of smoking and genetic susceptibility along with other factors such as diet and alcohol, which has reconceptualised the disease as a condition characterised by a multifactorial process (47, 63, 99).

Despite the advancements in recent years in the understanding of the pathogenesis of chronic pancreatitis, this progress has not been accompanied by widespread understanding on the population frequency of this disease. Knowledge is required on the population-distribution of chronic pancreatitis, the impact of imaging studies, environmental and other factors on disease estimates and trends between and within different populations.

Chronic pancreatitis is complicated by difficult diagnosis (115), unpredictable clinical course (125), and the development of associated consequences such as chronic pain (126), PEI and related malabsorptive symptoms (127), which contribute to reduced

quality of life (128). Many patients with chronic pancreatitis suffer PEI causing progressive malabsorption including macro and micronutrient deficiencies, and in many cases malnutrition is complicated by the presence of pathogenic bacteria in the small intestine (129, 130). These bacteria may cause co-existent malabsorptive symptoms which may reduce the efficacy of PERT (131), and may result in advancing or intractable symptoms. While there have been greats strides in research on PEI and PERT, there is less known about complications, such as bacterial overgrowth in the intestine, which lessen the efficacy of PERT, leading to worsening malabsorption (132). To add to this, few research efforts have focussed on the management of chronic pancreatitis, particularly in the primary care setting where the majority of patient care occurs. Patients with chronic conditions must have access to chronic disease management programmes, which are notably absent currently in the Irish healthcare sector, and again, particularly in primary care. These aforementioned factors bring to the fore significant deficits in current knowledge which should be addressed in order to provide a continuum of preventative, management and support mechanisms, to comprehensively manage this chronic disease and improve patient outcomes.

The last 30 years has seen advances and evolution of technologies including high-resolution CT, Magnetic Resonance Imaging (MRI) and endoscopic ultrasound (EUS), which are diagnostic tools of choice. Considering the poor sensitivity of older generation technologies, it is likely that many patients included in earlier epidemiological series were diagnosed after the disease was well established and in the presence of morphological changes such as fibrosis and calcifications. With advances in technologies, and the prevalent use of genetic susceptibility analysis, it is likely that chronic pancreatitis will now be diagnosed at earlier stages, using genetic information, and subtle pancreatic changes seen from radiological and endoscopic studies.

With this is mind, this chapter consists of a literature review of four keys chronic pancreatitis themes; epidemiology, chronic pancreatitis management, small intestine bacterial overgrowth, and genetics.

3.2. Epidemiology

Whilst there have been advancements in knowledge of the aetiology and pathogenesis of chronic pancreatitis, this has not been mirrored by reports of the epidemiology of chronic pancreatitis in many European countries. Outside of an epidemiological series conducted in Japan, data on incidence, prevalence and hospitalisation of chronic pancreatitis are sparsely reported. Difficulties arise when comparing epidemiological reports, due to differences in the use of diagnosis or classification criteria, and studies having been conducted at different time points. Single centre studies especially tertiary or referral centres run the risk of including the sicker and more complicated chronic pancreatitis patients, which may not be comparable to the whole population.

3.2.1.1. Prevalence

The prevalence of chronic pancreatitis worldwide is sparsely reported. In Europe, the prevalence of chronic pancreatitis is thought to range from 11.7-49.3 per 100,000 of population (133, 134). The prevalence of chronic pancreatitis appears to be increasing in Asian countries, where chronic pancreatitis epidemiology has been well-documented in a series of studies spanning over 40 years. The prevalence in Japan ranged from 28.5 to 52.4 per 100,000 in Japan (135-138) and from 3.08 to 13.52 in China (139). The prevalence in Southern India was found to be particularly high at 125 per 100,000 (140, 141). The prevalence of chronic pancreatitis in the US region of Minnesota was reported to be 41.8 per 100,000 of population (82).

3.2.1.2. Incidence

The incidence of chronic pancreatitis has been reported more frequently than the prevalence, although there is inter-country variability and differences in study design. European incidence rate range from the lowest 1.8 per 100,000 population in a single centre study (142) to 13.4 per 100,000 population (143) and this wide variation may be attributed to distinctly different study methodologies used. In the United States the incidence has increased only marginally from 3.3 per 100,000 of population in 1940-1969 (144) to 4.3 per 100,000 of population in 1996-1997 (82). However, there is a distinct paucity of nationwide epidemiological studies of chronic pancreatitis in the United States. In Japan, serial nationwide epidemiological survey data have shown that the chronic pancreatitis incidence is increasing and has risen from 5.4 per 100,000 in 1994 (136) to 14.4 per 100,000 in 2014 (135).

3.2.1.3. Hospitalisation

As expected, considering the increases in both incidence and prevalence in many countries, there have also been reported increases in hospitalisation rates for chronic pancreatitis. In England and Wales, hospital discharges increased considerably from 8.3 per million population in 1960-64 to 31.8 per million population in 1980-1984 (145). These findings were corroborated in a later regional study from England where hospitalisation rates for chronic pancreatitis doubled from 4.3 per 100,000 in 1989/1990 to 8.6 per 100,000 in 1999/2000 (41). Two European studies also reported increases in hospitalisation rates. In Finland the incidence of hospitalisations for chronic pancreatitis increased by 36% in the 10 years between 1979 and 1989 (143) and similarly a 75% increase was noted in the Netherlands from 1992-2004 (146). While these may be true increases, it is also plausible that improvements in diagnosis of chronic pancreatitis along with increased disease awareness among consultants over the years, has contributed to the observed increase in hospitalisation rates. It is also anticipated that

rising *per capita* alcohol use is correlated with increases in pancreatitis hospital admissions, and this will be discussed further in Chapter 6.

3.3. Management of chronic pancreatitis

3.3.1. Chronic disease management

Chronic diseases are long-term, progressive medical conditions lasting more than three months, which can be treated but not cured, and are associated with dysfunction and generally slow progression (147, 148). Chronic diseases require a long-term and complex response, coordinated by different healthcare professionals with access to necessary treatment, equipment, and medication in all healthcare settings. However, care tends to be primarily structured around acute episodes (149). Chronic diseases are a major issue, constituting a significant resource burden due to the length and complexity of treatments, frequent hospital admissions, risks associated with polypharmacy, and complex co-morbidities (150). Chronic disease patients are more likely to present at GP, emergency department and require hospitalisation than those without such illnesses. In Ireland, 38% of people over 50 years have one chronic condition, and 11% have two or more common chronic conditions (151). Furthermore, 65% of adults over the age of 65 years have 2 or more chronic conditions (152). Approximately 80% of all GP consultations, and 76% of hospital bed days used, are related to chronic diseases and their complications (3, 153). Additionally, it is estimated that only 10% of patients utilise 60% of healthcare resources (154). Considering the aging population worldwide, chronic diseases will undoubtedly increase proportionately. Chronic diseases are the main cause of the majority of all deaths in Europe, and worldwide (149), but despite growing evidence of epidemiological and economic impact, the global response remains inadequate (155). A key concept in

chronic disease management is prevention, and there is need to integrate health promotion and disease prevention into ongoing service delivery. Improving health and wellbeing is a priority for the government and the whole of society (156) and in terms of chronic pancreatitis disease management a key component of this is targeting smoking and alcohol use.

Chronic disease management represents one of the most difficult and critical challenges facing health services globally. Global spending on chronic disease management is fast becoming unsustainable, as healthcare systems struggle to deliver high quality care, to escalating numbers of patients, - many of whom have more than one chronic condition (149, 157). In clinical settings, chronic disease management should be an organised, proactive, multi-component, patient-centred approach to healthcare delivery, guided by health information from electronic medical records, made available in real-time from the main disease centres for populations (158). The Irish healthcare system and healthcare systems worldwide are experiencing increasing demand with chronic disease management. Considerable gaps in healthcare and safety, together with escalating costs are driving health service reform. The reform of chronic disease management is a priority for healthcare managers and healthcare policy makers where some limited success has been achieved, despite the absence of a generic healthcare model which is suitable for all healthcare systems (159). Given this background, chronic disease management is increasingly considered an important issue by policy-makers and researchers across Europe, with the search continuing for interventions and strategies to address chronic disease (149).

The urgent need for introducing substantial changes to the way care is delivered to chronic disease patients is widely accepted, therefore in response, many expert reports on tacking chronic disease have been published nationally and internationally. In Ireland, government backed national policies and frameworks aimed at preventing and managing chronic diseases have been published (3, 147, 152, 153, 158-162).

Organisational and improved clinical leadership will be necessary to support a change from reactive to more proactive patient-centred care. This change requires re-orientation of service delivery and associated or reallocated resourcing. The provision of interventions at patient level is not sufficient, and international evidence indicates that action must be taken at organisational and health professional level, including resourcing and coordinating the wider health system through partnership with GPs (161).

3.3.2. The current structure of chronic disease management in Ireland

Chronic disease management in Ireland is presently characterised by high levels of inequality. According the Health Service Executive of Ireland (HSE), the method by which care is provided for chronic disease patients is ineffective, inefficient, and ultimately unsustainable, with a heavy reliance on the need for hospitalisations for chronic conditions (163). Correspondingly, the HSE acknowledged that outpatient services are overstretched due to the dependence of chronic disease sufferers on such services, which results in delayed appointments for all patients, and may result in gaps in care as services struggle to meet growing needs (163). For many chronic conditions there is evidence that better primary care can reduce hospital admission, and that better hospital care, will reduce length of stay (164). In the UK, there are large variations in admission rates for patients with specific chronic diseases from different Primary Care Trust that serve the same population (164), - and there is no evidence to suggest that Ireland is dissimilar.

Historically in Ireland, the acute hospital system has been predominantly provider-driven, insufficiently based on population needs, and the main force behind service development has been hospitals responding to local and regional needs (159). Inevitably this has resulted in service gaps, geographical inequalities, inefficiencies,

duplication, quality issues, and a systemic preoccupation on workforce/institutional concerns, rather than planning and prioritising services around population health needs (159). The Primary Care Strategy (160), which was published by the Irish government in 2001, represented an opportunity to achieve the development of primary care service for all health users in Ireland. While some objectives have been achieved, there has been little deliberate action, or investment in services. Therefore, reform is required to augment primary care services, which are central to any strategy to address population health needs. Planning and realignment of services between secondary and primary care is required to provide more integration and linkage. A key requirement of reform is to build a model of care, focussed on the provision of integrated care as much as possible in primary care, with high standards of patient safety (159). At present healthcare systems are reactive, organised to deal with acute illness and injury with the patient playing a passive role (165). Acute hospital care will always be an essential dimension of any health service, however, it must be provided in an integrated model which seeks to avoid unnecessary hospitalisation (159). The move is required towards earlier care delivered to patients in the community, rather than delayed care delivered to patients admitted into hospital settings. National policy favours shifting care from hospital to primary care, however, an agreed delivery model is yet to be defined (150).

In Ireland, patients with chronic diseases are faced with another significant obstacle to optimum disease management. Ireland is unusual compared to the majority of countries in Europe, in that universal access to GP services are not available (166). The European Observatory on Health Systems and Policies, conducted a recent review on primary care services and found that the highest formal payments exist in Ireland, with non-medical card holders paying up to €65 per visit, without reimbursement (166). There is a fundamental issue in terms of accessibility and equity in those chronic pancreatitis patients with incomes above the threshold eligibility for GMS card. On the other hand GMS cardholders are discriminated in terms of accessing specialised services and incur longer waiting times. There are also inequalities for public and

private patients' chronic pancreatitis with regard to access, waiting times, and cost. Patients with chronic diseases such as chronic pancreatitis, which require multiple healthcare services encounters for disease management, face inherent obstacles to care. In 2001, the Irish government (167) committed to universal health insurance for all patients by 2016, which would end the *"unfair, unequal and inefficient two-tiered health system".* Unfortunately, to date this has not transpired. Privately funded patients remain financially discriminated in terms of access to GP, and public patients experience discrimination in relation to access to hospital services including routine OPD access, diagnostics and elective in-patient care.

The World Health Organisation (WHO) has recommended the Chronic Care Model (CCM) to guide worldwide healthcare system reform (168, 169). CCM is an internationally recognised evidence-based theoretical model which identifies the essential elements of a healthcare system that encourages high quality chronic illness care (165, 170). According to WHO, coordination across care setting and providers is more effective than single or uncoordinated intervention (2). The underlying principle of CCM enables healthcare providers and patients to deal proactively with chronic illness, leading to patients receiving better care, improved clinical outcomes and quality of life, - resulting in reduced need for healthcare in the future (171). Government policies and targets for acute sector management and health consumers such as reducing waiting lists and increasing productivity are strongly focussed on the elective care sector (164). There is a significant need for a new coordinated national approach that helps people with chronic diseases, and their carers, manage their conditions more effectively, thus reducing the burden of chronic diseases on the health services (164).

3.3.3. Patient self-management and chronic disease

Patients who have chronic diseases, should be supported in self-management of the disease and assisted by ongoing care and education (172). All chronic conditions are known to be significantly more prevalent amongst those from lower levels of education, and in lower socioeconomic groups (153). Supporting patients to self-manage their health conditions can help to improve outcomes, and entails the systematic provision of education and supportive interventions (173). This in turn increases patients skills, and confidence, which results in improved outcomes for patients ranging from enhanced quality of life, to better clinical outcomes and reduced healthcare utilisation which includes hospitalisation (173). Self-management interventions and psychological interventions such as cognitive behavioural therapy have been shown to be effective in reducing pain and pain impact in gastrointestinal disorders (174). Despite their relevance and utility in other painful chronic conditions, the uses of such self-management techniques have not been evaluated in chronic pancreatitis patients.

3.3.4. Chronic pancreatitis in hospital-based care

The majority of chronic pancreatitis patients are treated on an outpatient basis, however, significant numbers of patients are hospitalised (175). Chronic pancreatitis patients require hospital admission for a range of services including; investigations, diagnosis, treatment, radiologic / endoscopic studies, interventional pain medicine, surgery, dietetic assessment, bone health, and management of disease-associated multi-morbidities. There are a large number of evidence-based clinical recommendations and guidelines available, which instruct all aspects of hospital-based chronic pancreatitis patient care including; diagnosis, treatment, nutrition and endocrine management, bone health, surgical and endoscopic intervention. None of the available

guidelines on the management of chronic pancreatitis instruct the care of patients outside of the acute care setting. This is an area which urgently requires attention.

3.3.5. Chronic pancreatitis in primary care

Patients who experience acute exacerbations of chronic pancreatitis usually need to attend hospital for treatment, but in the absence of urgent events, patients are managed in the outpatient and community settings. There are many important facets of chronic pancreatitis which are managed in the primary care setting, with input from secondary care services. Chronic disease management is ideally situated in general practice, with access to general practitioners, practice nurses, dietitians, psychology, and services which are crucial to the management of chronic pancreatitis. Primary care and associated services should be further strengthened as a medical hub with specialty care feeding in. However, in a recent survey of chronic disease management in primary care, GPs highlighted that significant changes were required to make chronic disease management work (176). International literature on successful chronic disease care, points to key infrastructural elements in primary care including; disease registries, information systems, use of guidelines and greater interaction between primary and secondary care (177). The development of better primary care structures and integration between primary and secondary care can play a significant role in reducing the use of expensive and disruptive hospital stays for people with chronic diseases (164). GPs and people who attend them for care will need improved and acceptable safe levels of service from secondary care, and deliberate government backing, to provide accountable, good quality chronic disease management (176).

3.3.6. Chronic pancreatitis and emergency departments

Chronic pancreatitis patient may require urgent medical attention for a first time attack, acute flair-up, or symptom exacerbation. Often, in the absence of availability of GP (i.e. out-of-hours treatment, no GP access) patients may attend the accident and emergency department for care. As standards of care differ substantially across different hospitals and healthcare settings, chronic disease patients are thus vulnerable to unplanned or non-negotiated changes in management protocols, which interrupt care. This could happen frequently with repeated unplanned admissions to several emergency rooms in different regions. In fact both the burden of chronic pancreatitis on the emergency care sector in Ireland is unknown, as is the extent to which people acutely present to their GP or local emergency department for urgent acute unscheduled care. This constitutes a significant research gap which should be addressed.

3.4. Small intestinal bacterial overgrowth syndrome

Along with abdominal pain, the most common clinical complaint among patients with chronic pancreatitis is progressive PEI. In PEI, reduced production and secretion of pancreatic enzyme causes malabsorption of micro and macronutrients. The mainstay treatment and management of PEI is PERT. However, in many patients with chronic pancreatitis-related PEI, enzyme replacement therapy is insufficient (178, 179). Among the reasons for limited efficacy of PERT in chronic pancreatitis is secondary enteritis with bacterial overgrowth in the small intestine (180). The human gut microbiota is considered the largest organ of the body, serving a number of important functions. Alteration or change in bacterial location is known to be associated with several diseases. In chronic pancreatitis patients with intractable gastrointestinal symptoms despite clinically adequate PERT regimes, SIBO and other conditions such as giardiasis and coeliac disease should be out-ruled (130, 131, 181).

3.4.1. SIBO definition

SIBO is described as an increase in the number of bacteria and/or alteration of the type of these bacteria, which typically causes nutrient malabsorption in the proximal small bowel.. The most commonly cited definition of SIBO is the presence of 10^5 or more colony forming units per millilitre (CFU/ml) of bacteria, usually colonic enterobacteria, grown from jejunal aspirate culture (182). This value of this definition has been questioned in recent times in consensus conference and systematic review due to its applicability to common gastrointestinal conditions (183, 184). This current definition of SIBO, is based on the aspiration findings from stagnant loop (185). Normal subjects rarely exceed 10^3 CFU/ml in the upper intestine, and arguably this may be a more suitable defining threshold for gastrointestinal conditions (132, 184) .

3.4.2. Aetiology

There are several intrinsic defence mechanisms that prevent the overgrowth of intestinal bacteria including; gastric acid secretion, intestinal motility, intact ileo-caecal valve, immunoglobulins in intestinal secretions, and the antibacterial properties of pancreatic and biliary secretions (186). The aetiology of SIBO is complex and is associated with disorders that result in failures of the protective antibacterial mechanisms (such as achlorhydria, PEI, and immunodeficiency syndromes), anatomical abnormalities (such as small intestinal obstruction, diverticula, fistula, surgical blind loop, and ileo-caecal resection), and motility disorders (such as scleroderma, autonomic neuropathy in diabetes mellitus, and small intestine pseudo-obstruction)(129). In some cases, multiple aetiological and predisposing factors exist. Furthermore, in some patients the underlying disease is complicated by SIBO, which in turn causes further deterioration in the underlying condition. SIBO occurs most

commonly in either patients with small intestinal mobility disorders or those with chronic pancreatitis, which together account for 90% of all cases (129).

3.4.3. Clinical presentation

Patients with SIBO may be clinically asymptomatic, or may have symptoms that resemble irritable bowel syndrome, such as; bloating, flatulence, abdominal discomfort, diarrhoea, abdominal pain (129). In more severe cases; malabsorption (weight loss, steatorrhea, malnutrition), liver lesions, skin manifestations (rosacea), arthralgia and deficiency syndromes (including; anaemia, tetany, metabolic bone disease, impaired gut barrier function) may occur (129). Symptoms of SIBO develop due to; protracted inflammation, immune activation, alteration in motility, increase in intestinal permeability, bile salts deconjugation, secondary lactase deficiency, water and nutrient malabsorption with increasing osmotic load and luminal contents (187, 188). SIBO should be considered in all cases of non-specific dyspeptic complaints (bloating, abdominal discomfort, diarrhoea, abdominal pain), in motility disorders, anatomical abnormalities of the small bowel and in malassimilation syndromes (malabsorption, maldigestion) (129, 184, 189, 190). Some intestinal disorders may mimic SIBO, and should be considered in differential diagnosis. Therefore, it is always necessary to consider SIBO in the case of unexplained deterioration of diseases such as Crohn's Disease, chronic pancreatitis and scleroderma (129).

3.4.4. Prevalence

The prevalence of SIBO in the general healthy population is unknown. Initially thought to only occur in a small number of patients, it is now apparent that this disorder is more prevalent than previously thought. Measurement of true prevalence may be difficult due to the association of SIBO with a number of other conditions. This is clear in the case

of chronic pancreatitis, where the clinical symptoms are similar to that of PEI including; abdominal pain, diarrhoea, bloating, excessive flatulence and steatorrhea (191). The reported prevalence of SIBO in chronic pancreatitis is wide ranging from 0% to 92% (192, 193). A recent systematic review reported that there is considerable heterogeneity amongst the available studies on SIBO in CP (194). Some of the available studies recruited small numbers of patients, heterogeneous patient types, or were uncontrolled. Some did not utilise the recommended test and substrates for the detection of SIBO (183).

3.4.5. Pathogenesis

In the healthy human host, small bowel microorganisms are isolated from the upper respiratory tract through the forward barrier, and from the colon through the backward barrier (195). In the upper gut, the microbes are predominantly those which can resist gastric acid such as *Helicobacter pylori* and *lactobacilli*. The distal small bowel and colon have more microbes (10^7 to 10^{12} CFU/ml) which consist of coliforms (gram negative bacilli that ferment lactose) which are present exclusively in the distal gut (187). The concentration of bacteria in the small bowel is generally multiple magnitudes lower than the large bowel due to microenvironment and anatomical differences between the two (184). The role of the gut microbiota is several fold; as a barrier to pathogenic organisms, for regulation of immune function and motility, food digestion, short-chain fatty acid production, production of vitamins, metabolism of drugs, detoxification of toxic compounds, and for the maintenance of gastrointestinal tract homeostasis (187, 196, 197).

The small intestine is accessible to non-residing bacteria from the mouth and ingested foods, from the upper respiratory tract, and from reverse bacteria from the colon, depending on which barrier mechanism is interrupted. The high concentration of

bacteria interferes with normal small bowel nutrient absorption, and patients develop malnutrition and gastroenterological symptoms such as diarrhoea, steatorrhea, and also macrocytic anaemia (191). The growth of a large amount of bacteria in the small intestine produces non-specific macro and microscopic mucosal inflammation, with resultant epithelial changes, such a blunting of the villi, and damage to the brush border (198). When gastric acid secretion is reduced or diminished, gram positive bacteria from the upper respiratory tract are mainly responsible for SIBO (183). Medications such as proton pump inhibitors, autoimmune or *Helicobacter pylori*-associated mucosal atrophy, malnutrition, and gastrectomy are the predominant causes of failure of the forward barrier (195). When intestinal clearance is impaired or ineffective, intestinal bacterial overgrowth is predominantly from colonic-type bacteria, mainly gram negative aerobes (183). This usually occurs in the context of impaired intestinal motility and mechanical stasis, altered intestinal anatomy (surgery) and in the case of immune dysfunction (132).

Multiple factors exist as to the occurrence of SIBO amongst chronic pancreatitis patients including; the absence of anti-bacterial effect of proteolytic enzymes, abnormal chyme in the small intestinal lumen, intestinal stasis or dysmotility, multi-drug administration, surgery, and ongoing alcohol consumption (129). Achlorhydria results from chronic gastritis and treatment with long term use of proton pump inhibitors increases duodenal bacteria and accelerates intestinal transit; both of these factors may further increase susceptibility to bacterial overgrowth (129, 186). Significant numbers of cystic fibrosis patients experience pancreatitis pathology with pancreas insufficiency, and the prevalence of SIBO amongst this disease cohort is similarly high and thought to be approximately 56% (199).

3.4.6. SIBO diagnosis

Traditionally, aspiration and culture of duodenal fluid was considered the gold standard for SIBO diagnosis, however, this method is not often utilised in clinical practice due to the invasive nature, the need for endotracheal intubation and the high risk of contamination of sample. A recent systematic review of diagnostic techniques for SIBO, revealed that no gold standard diagnostic test exists (184). Aspiration-based methods of diagnoses, are invasive, cumbersome, and expensive, and are therefore infrequently used in clinical practice. In addition, there is no clarity regarding the microbiological cut-offs that define a positive culture, and there are technical difficulties associated with transport and culture of aspirate (200). Owing to the invasive nature of direct aspiration techniques, indirect tests (breath-testing) have been developed which nowadays are preferred in clinical practice to detect SIBO presence. Breath tests are non-invasive, easy to use, and cost-effective alternative to aspiration and culture. Hydrogen breath tests are most frequently used to diagnose SIBO, which are based on the assumption that the only source of hydrogen production in the body is from fermentation of carbohydrates by GI microbiota (201). Commonly used substrates for breath-testing include; glucose and lactulose, with the former having the most diagnostic accuracy (183, 202). Diagnostic tests are neither very sensitive nor specific, and therefore a high degree of clinical suspicion is required to diagnose SIBO (187). In the absence of a validated gold standard diagnostic test the most practical method to evaluate SIBO is; a test, treat and outcome-evaluation technique (184).

3.4.7. Breath-testing

All methods of breath testing rely on the collection and quantification of expired air produced by bacterial metabolism of an ingested substrate. Hydrogen breath tests are based on the determination of hydrogen concentration in expired air as hydrogen and methane are produced by fermentation of intraluminal substrates (carbohydrates) by

bacteria contaminating the small bowel (183). The measurement of breath methane excretion is not currently recommended to improve diagnostic accuracy of the hydrogen breath test (183). In a healthy person, glucose is completely absorbed in the small intestine before reaching the colon, without producing hydrogen or methane elevation (203). If SIBO is present, glucose will be metabolised by small bowel bacteria prior to absorption which will produce a hydrogen or methane peak. Glucose hydrogen breath tests (GHBT), show a single 'early' peak of hydrogen excretion indicating the metabolism of the ingested substrate by bacteria in the small intestine.

Lactulose is a non-absorbable disaccharide which passes unabsorbed through the small bowel and into the colon. Lactulose hydrogen breath testing (LHBT), assumes that an early peak (typically within 90 minutes), or a double peak (first due to small bowel fermentation, and second from colon entry), is diagnostic of SIBO (204). However, it is thought that 50% of healthy individuals have a rise in hydrogen excretion within the first 90 minutes, reflecting variations in transit time (205). Further, the double-peak criterion is quite insensitive for SIBO diagnosis (204, 206). Therefore, the use of LHBT is known to result in fallaciously high rates of positivity, and is not recommended in clinical practice to detect SIBO. A number of studies have shown LHBT to be inappropriate for the detection of SIBO (207-210). GHBT is more acceptable for the diagnosis of SIBO, as the commonly accepted double-peak criterion of LHBT is very insensitive and the recently described early peak is often a false positive (204).

In some cases, false negative hydrogen breath tests occur and this may be due to the absence of hydrogen-producing bacteria or a low increase in hydrogen production. In the case of LHBT, the first 'early' hydrogen peak can merge with the late 'colonic' peak resulting in a false negative. In the case of GHBT, quick absorption of glucose in the proximal bowel may result in a false negative. Moreover, false-positive hydrogen breath tests have been reported in individuals with accelerated intestinal transit time (183).

Diagnostically, GHBT is more accurate than LHBT (183). However, all methods of SIBO diagnosis require consideration in the context of clinical symptoms, treatment, and clinical symptom response.

3.4.7.1. Glucose hydrogen breath testing (GHBT)

GHBT is a useful, non-invasive and inexpensive test to diagnose SIBO. For accurate SIBO diagnosis there must be careful patient preparation, strict protocol adherence, and careful interpretation of results, supported by accurate evaluation of the patient's clinical condition.

The most commonly cited substrate dose administration and test length for GHBT are;

(1) Glucose 50g per 250ml; 120 minute

(2) Glucose 75-100g (in different concentrations); 120 minutes

(Summary of Rome Consensus on glucose HBT protocol) (183)

The diagnostic accuracy for GHBT is approximately 72%, and it is thought that increasing the substrate dose and extending the test length may also increase exposure to the distal segment of the small intestine therefore enabling distal SIBO diagnosis (183). However, increasing the test substrate from 50g to 75-100g, along with increasing the test duration, has not shown a significant improvement in sensitivity (206).

3.4.8. Malabsorption related to SIBO

In general, malabsorption as a result of SIBO can be attributed to the intraluminal effects of proliferating bacteria, combined with damage that occurs to the small bowel

enterocytes (191). Disturbance and alteration of bacterial composition, may lead to bacterial overgrowth, which can in turn lead to profound malabsorption in the proximal small bowel (130). This is of significant importance in the context of diseases such as chronic pancreatitis, which are characterised by underlying malabsorption. Various functional consequences of intestinal damage have been reported including; diminished disaccharidase activity, decreased transport of monosaccharides, amino acids, fatty acids, and protein-losing enteropathy (211). Steatorrhoea in SIBO, occurs due to deconjugation of bile salts and impaired transport of lipids through the damaged small bowel enterocytes (191). Vitamin B_{12} (cobalamin) malabsorption in SIBO results in macrocytic and microcytic anaemia and in severe prolonged cases can cause neurologic damage including; posterolateral spinal cord demyelinization, peripheral neuropathy and cerebral cognitive defects (191). Malabsorption of fat-soluble vitamins results in night blindness (vitamin A), osteomalacia and hypocalcaemia tetany (vitamin D), coagulopathy (vitamin K) or vitamin E deficiency syndromes (neuropathy, T cell abnormalities) (191, 212).

3.4.9. Other patient groups at risk of SIBO development

3.4.9.1. Patients with diabetes mellitus

SIBO is a notable complication amongst patients with diabetes due to diabetic neuropathy and delayed gastric emptying. Many factors restrict bacterial cell growth in the small intestine including; bacterial role of gastric acid, digestive enzymes, bile salts, peristalsis, and secretory IgA (213). Diabetic autonomic neuropathy, may result in delayed gastric emptying and intestinal motility disturbances, - which may lead to SIBO (213, 214). In diabetes, the occurrence of SIBO is characterised by significant malabsorption of vitamins and essential nutrients, that is more profound than in the healthy population (130). In the absence of SIBO, glucose is absorbed in the intestine,

and no bacterial fermentation occurs. However, in SIBO positive diabetic patients, acute hyperglycaemia resulting from glucose malabsorption in the small bowel, may require a major insulin dosage (213) Transit disturbances can result in altered metabolic conditions. This may account for higher insulin requirement in diabetic patients (213).

3.4.9.2. Elderly patients

Major risk factors predisposing to SIBO development include achlorhydria, small bowel diverticulosis, reduced gastrointestinal motility and gastrointestinal surgery, factors which tend to be prevalent in the elderly (130). SIBO is known to occur in the elderly without any evident underlying small intestinal pathology (129). SIBO can precipitate malnutrition in the older population, and is associated with weight loss and lower body mass index (BMI). Weight increase follows treatment with a course of antibiotics (130).

3.4.10. Treatment of SIBO

The therapeutic approach to SIBO is orientated towards resolving underlying and predisposing conditions, and is supported by antibiotic treatment aimed at the restoration of normal small intestinal microflora, along with modification of dietary habits for symptomatic relief (195). In many cases, the treatment of structural defect or underlying disease cannot be achieved (for example, surgical resection may not be reversed), which is similar in the case of intractable PEI in many chronic pancreatitis patients. Management principles should include the correction of nutritional deficiencies if present, which may include; the supplementation of fat-soluble vitamins, vitamin B12, and minerals. The use of prokinetics may also be considered to treat intestinal dysmotility (200). The mainstay of SIBO treatment is by antibiotic therapy. Many antibiotic regimens have been advocated for the treatment of SIBO, and effective treatments are those with an ability against aerobic and anaerobic enterobacteria

(200). Two recent systematic review and meta-analyses demonstrated the efficacy and short-term safety of the use of Rifaximin (a non-absorbed rifamycin structural analogue which has a broad antimicrobial spectrum) in SIBO treatment (215, 216). Additionally, in a meta-analysis of antibiotic therapy for SIBO treatment, antibiotics were shown to be effective for normalisation of breath-tests in SIBO-symptomatic patients, and Rifaximin had a test-normalisation rate of 49.5% (217).

3.4.11. Prognosis

SIBO is considered to be associated with a relatively high recurrence rate which is dependent on many underlying factors such as old age, chronic use of proton pump inhibitors (PPIs), and history of appendectomy (218). SIBO was found to reoccur in 44% of patients nine months after successful antibiotic treatment with Rifaximin (218). Recurrence of SIBO symptoms after antibiotic treatment is not uncommon. One study showed 30% of patients treated with Rifaximin had SIBO recurrence at 6 months (218). Treatment response, antibiotic resistance and efficacy are areas which require further investigation.

3.5. Genetics

3.5.1. Overview of gene mutations in chronic pancreatitis

In recent years there has been increasing recognition of the causative role of genetic variants in the development of chronic pancreatitis, both idiopathic and alcohol-associated. The principal susceptibility genes currently known are; cystic fibrosis transmembrane conductance regulator gene *(CFTR),* serine protease inhibitor kazal type-1 *(SPINK1),* cationic trypsinogen *(PRSS1)*, chymotrypsin C *(CTRC),* and calcium-sensing receptor *(CASR),* and variants affecting both coding and regulatory sequences

have been related with disease (101). An overview of role of these mutations is provided in Table 3.1. The strongest risk factors are associated with genetic variants in *PRSS1*, *SPINK1* and *CFTR*, and to a lesser extent *CTRC* and *CASR.* The latest research shows that a single factor rarely causes pancreatitis, and the majority of patients with recurrent acute and chronic pancreatitis have multiple variants in a gene, or epistatic interactions between multiple genes, coupled with environmental stressors (219).

In 1996, a breakthrough in the understanding of recurrent acute pancreatitis and chronic pancreatitis came with the discovery that gain-of-function mutations in the gene that encodes *PRSS1* (variant R122H) causes hereditary pancreatitis (51, 220). This linkage represented a major achievement in advancing the understanding of the genetic basis of hereditary pancreatitis, which is characterised by recurrent episodes of acute pancreatitis and chronic pancreatitis. Autolytic peptide bonds in trypsin play a role in degradation of prematurely activated trypsin in the pancreas. R122H is known to destruct this 'failsafe' mechanism which prevents premature activation, which in turn increases intrapancreatic trypsin activity, and eventually causes pancreatitis (51, 221). This firmly established the critical role of trypsinogen in the pathogenesis of chronic pancreatitis (51). Gain-of-function mutations have subsequently been detected in the *PRSS1* gene in idiopathic chronic pancreatitis patients (222, 223). This also prompted the use of the candidate gene approach to explore possible disease associations.

The pancreatic lesions of cystic fibrosis (which are developed *in utero*) were observed to closely resemble chronic pancreatitis pathology. In 1998, this stimulated the exploration of the possible association between mutations of the cystic fibrosis-causing gene, *CFTR*, and chronic pancreatitis (103, 104). This led to the discovery that about 20% of patients with idiopathic chronic pancreatitis bear at least one *CFTR* mutation. Two severe *CFTR* (duct cell) mutations are widely known to lead to cystic fibrosis. In 1998, two research groups reported that severe *CFTR* variants were commonly seen in

chronic pancreatitis patients who lacked the pulmonary pathology typically seen in cystic fibrosis patients (103, 104). Because *CFTR* is expressed in the pancreatic duct cell, this indicates that CFTR- mediated pancreatic disease is initiated in the duct cell, rather than the acinar cell, even though the phenotypic features are the same for other forms of chronic pancreatitis (219). These findings have been replicated in studies in the US (224), and Europe (225, 226). *CTFR* carrier status is associated with increased liability to develop chronic pancreatitis with increased odds ratios of 2.9-4.5 (226). Differential gene associations are seen with alcohol-associated and idiopathic chronic pancreatitis forms.

In 2000, mutations in the serine protease inhibitor *SPINK1* gene were found to be strongly associated with idiopathic and familial forms of chronic pancreatitis (102). Genetic factors are very important as patients that are genetically predisposed, such as carriers of *CFTR* / *SPINK1* mutations or mutations in the key genes in the inflammatory pathways, will have a more prominent and sustained inflammatory response. They will also be more susceptible to the anti-inflammatory cascade and have more rapid progression to fibrosis (227). The pathogenesis of chronic pancreatitis remains only partially understood. There are several mechanisms known to be factors including; duct obstruction by protein plugs, diet, ethanol-direct toxicity, and oxidative stress (125, 228). The exact mechanism of alcohol pancreatitis is not known. Since only a small percentage of heavy drinkers develop pancreatitis, many studies have suggested that alcohol only represents a risk factor for the development of pancreatic inflammation, in genetically or environmentally predisposed individuals (229-231). Approximately one third of all cases are idiopathic, and disease development is not attributable to any aetiological risk factor. Therefore there must be a genetic predisposition. It therefore appears that genetic influences may be important in a significant proportion of chronic pancreatitis cases. It is likely that other genes are yet to be discovered given that only minorities of patients, perhaps up to 50% of cases, have a known associated mutation

to date. Further evaluations of factors associated with pathogenic variants in patients with idiopathic and alcohol-induced chronic pancreatitis are required. The discovery of several genetic susceptibility genes and disease-modifying variants not only provides insights into the molecular mechanisms of pancreatitis, but are also potentially powerful diagnostic tools. Information derived thus far has important implications for disease mechanism, and some variants show protective effects which could potentially provide therapeutic approaches. Moreover, potential treatment strategies may prevent the development of advanced chronic pancreatitis.

Genes	Short name	Details
Cystic fibrosis transmembrane conductance regulator gene	CFTR	*CFTR* is an ion channel that conducts chloride and bicarbonate across epithelial cell membranes. Mutations in *CFTR* diminish ion channel function and lead to impaired epithelial fluid transport effecting organs such as the lungs and pancreas
Serine protease inhibitor Kazal type 1 (also known as) pancreatic secretory trypsin inhibitor gene	SPINK1	*SPINK1* encodes a protein which is a trypsin inhibitor, which is secreted from the pancreatic acinar cells into pancreatic juice. It functions in the prevention of trypsin-catalysed premature zymogen activation within the pancreas and pancreatic ducts. Mutations in *SPINK1* are associated with pancreatitis
Cationic trypsinogen gene	PRSS1	*PRSS1* gene encodes a serine peptidase enzyme, which cleaves proteins into smaller parts. It is produced in the pancreas and helps with the digestion of food. Gain-of-function mutations in *PRSS1* are known to cause chronic pancreatitis
Chymotrypsin C gene	CTRC	*CTRC* plays an important role in trypsin activation and degradation. Loss-of-function variants in *CTRC* gene (which encodes the digestive enzyme Chymotrypsin C), are a risk factor for chronic pancreatitis (105, 106)
Calcium sensing receptor gene	CASR	The calcium-sensing receptor is a protein-coupled receptor that plays a key role in calcium homeostasis, by sensing extracellular calcium levels and is expressed in the parathyroid, bone, intestine, brain and both acinar and duct cells of the pancreas (219, 232). Mutations in *CASR* may lead to susceptibility to chronic pancreatitis.

Table 3.1: Overview of principal susceptibility genes in chronic pancreatitis

3.5.1.1. Trypsin pathway to pancreatic injury

As described in Chapter 1, pancreatic acinar cells are responsible for synthesis, storage and secretion of digestive enzymes. Enzymes are produced in precursor molecules which are packed into granules called zymogens, which are inactive until they reach the duodenum. Under normal conditions, defensive mechanisms are sufficient to protect the acinar cells from premature or inappropriate activation of digestive zymogens. Intrapancreatic zymogen activation leads to the activation of trypsin and other digestive enzymes which can be detrimental. Trypsinogens are synthesised as pre-pro-enzymes (pre-trypsinogens), containing a single peptide of 15 amino acids, followed the trypsinogen activation peptide, which is an 8 amino acid long pro-peptide (233). Upon entry into the endoplasmic reticulum lumen, the signal-peptide is removed and the zymogens are packaged as zymogen granules, which are secreted into the pancreatic juice. Trypsinogen activation from trypsin takes place in the duodenum by the brush border enteropeptidase which removes the activation peptide. Autoactivation of trypsinogen by trypsin in the pancreas is thought to result in pancreatitis. Elevated levels of active trypsin in the pancreas elicit disease onset and drive progression and the combined effects of mutations in several susceptibility genes determine intrapancreatic trypsin activity (234). To avoid auto digestion, two inhibitory mechanisms are present;

1. If trypsinogen is activated within the acinar cell, it can be inhibited by *SPINK1*. *SPINK1,* inhibits approximately 20% of trypsin activity (51). The amount of trypsinogen present greatly outnumbers the number of *SPINK1* molecules, therefore if more trypsinogen is activated than *SPINK1* can inhibit, then other protective mechanisms must be employed (49).
2. If *SPINK1* fails to inhibit trypsin, trypsin-like enzymes (for example, mesotrypsin) are activated which hydrolyse trypsin and other enzymes (231).

However, if there are mutations in the *SPINK1* or mesotrypsin genes, then protection mechanisms through trypsin inhibition method is delayed. The destruction of acinar cells leads to activation of several inflammatory cells such as macrophages and granulocytes which secrete pro-inflammatory cytokines. Mutations in cationic trypsinogen *(PRSS1)* that increase autoactivation are thought to be strong risk factors for chronic pancreatitis, and have typically been associated with hereditary pancreatitis. Protective mechanisms in the pancreas that curtail trypsinogen activation, and therefore reduce trypsin activity, involve either a trypsin inhibition, or trypsin degradation (234).

3.5.2. Serine protease inhibitor Kazal type-1 (SPINK1) associations with chronic pancreatitis

SPINK1 codes for the pancreatic secretory trypsin inhibitor, which is an acute phase protein and specific trypsin inhibitor. *SPINK1* is not normally expressed in the acinar cells, but is expressed in the context of ongoing inflammation. It is therefore a critical feedback inhibitor in the case of pancreas injury in inflammation, typically initiated by trypsin activation (219). Since *SPINK1* encodes a protein that guards the pancreas from the effects of recurrent or persistent trypsin activation, it is not a typical susceptibility gene for acute pancreatitis but rather a susceptibility gene for the chronic pancreatitis that follows acute pancreatitis (235). Meta-analyses by Aoun *et al* (236) tested the hypothesis that *SPINK1* mutations were a stronger risk factor in cases of chronic pancreatitis, not associated with alcohol or smoking, but associated with recurrent trypsin activation. The authors discovered that idiopathic chronic pancreatitis is significantly more strongly associated with *SPINK1* mutations than alcohol related injury, suggesting that idiopathic forms occur through trypsin activation mechanism (219, 236).

3.5.3. Cationic trypsinogen (PRSS1) and chronic pancreatitis

The human pancreas produces the digestive enzyme trypsinogen in three isoforms, - *PRSS1*, anionic trypsinogen *(PRSS2)* and mesotrypsin *(PRSS3)*, with *PRSS1* and *PRSS2* making up the bulk of trypsinogens in pancreatic juice and *PRSS1* is among the most abundant molecules produced by acinar cells (237). *PRSS1* plays an essential role in hydrolysing dietary proteins, at lysine and arginine amino acid residues. It also plays a key role in activating all other digestive enzymes (237). Several studies have discovered mutations in *PRSS1* in idiopathic or hereditary forms of chronic pancreatitis. Such mutations account for approximately 19% of patients assumed to have idiopathic chronic pancreatitis worldwide (238, 239). The mode of action is that mutations increase trypsin activity within the pancreatic parenchyma. About 20 mutations are known to be gain-of-function mutations which are mainly clustered around calcium-binding sites which regulate trypsin activation and inactivation (240), and are identified in about 80% of hereditary pancreatitis forms (219). It is important to note that *PRSS1* mutations all cause the same biochemical phenotype of increased autoactivation resulting in increased trypsin concentrations (234). The most common *PRSS1* mutations reported worldwide are R122H and N29I, which have been reported in Europe, North America and Asia (241).

3.5.4. Overview of cystic fibrosis

Chronic pancreatitis is a recognised complication of cystic fibrosis which is the most common inherited life-threatening genetic disorder among Caucasians. The disease affects multiple organs including the pancreas, the lungs, intestines, sweat glands and male reproductive glands. Despite being a multi-organ disease, pulmonary infections are the most common cause of morbidity and mortality (242). Cystic fibrosis is

characterised by mutations in the *CFTR* gene, which is located on chromosome seven and encodes for an adenosine triphosphate (ATP)-driven pump that transports sodium and chloride ions across epithelial surfaces (243) and is localised to the apical plasma membrane of epithelial cells. The *CFTR* protein functions as a channel for the movement of chloride ions in and out of cells, which is vital for electrolyte balance on epithelial surfaces, such as the lungs and pancreas. There are many different mutations in the *CFTR* gene which cause cystic fibrosis, and they are divided based on their effect on the *CFTR* protein. Nearly 2000 variants in *CFTR* have been identified, but little is known about their functional effects. An accepted molecular classification strategy organises variants by their effect on *CFTR* function which is demonstrated in Figure 2.1. Mutations in the *CFTR* gene result in absent or defective *CFTR* protein chloride channel function (243). Cystic fibrosis is caused by inheriting two severe pathogenic variants of *CFTR*, - mutations that eliminate effective chloride conductance.

The most common disease-causing mutation, which accounts for 66%-70% of cystic fibrosis chromosomes worldwide gives rise to a deletion of a single amino acid phenylanine at position 508 (F508del) on *CFTR* (244). In Ireland, 91.6% of cystic fibrosis patients have this FR508del mutation, on one or both *CFTR* alleles (245). The features of *CFTR*-associated diseases depend on the functional consequences of specific pathogenic variants on two *CFTR* alleles, as well as modifier genes, and effects on environmental factors (235).

Pancreatitis is a well-known but uncommon manifestation in cystic fibrosis and 85%-90% of patients with a severe *CFTR* mutation on both alleles – have PEI (246). In cystic fibrosis there is progressive pancreatic damage (beginning in utero and continuing to childhood), which results in complete loss of acinar tissue (247). Pancreatitis is thought to rarely occur in cystic fibrosis patients who are pancreatic insufficient (due to the absence of acinar tissue), but is common in pancreatic sufficient

patients (248, 249). However, research shows that only a minority of pancreatic sufficient cystic fibrosis patients develop pancreatitis, which supports the potential contribution of the type and severity of *CFTR* mutation, to pancreatitis risk (246).

According to registry data, Ireland has one of the highest prevalence rates of cystic fibrosis in the world, with over 1,461 diagnosed patients (245). The prevalence of cystic fibrosis at 2.98 per 100,000 population is the highest in Europe as is the incidence of 1:1353 based on registry data (250). Cystic fibrosis carriers have a frequency of 1:19 of the general population in Ireland - also the highest in the world (250). It is not inconceivable that these patients have an underlying genetic predisposition. This may predispose patients to pancreatic harm and may be exacerbated by alcohol, or other environmental toxins, such as smoking, - and when exposed, patients may be at significantly increased risk for the development of pancreatitis.

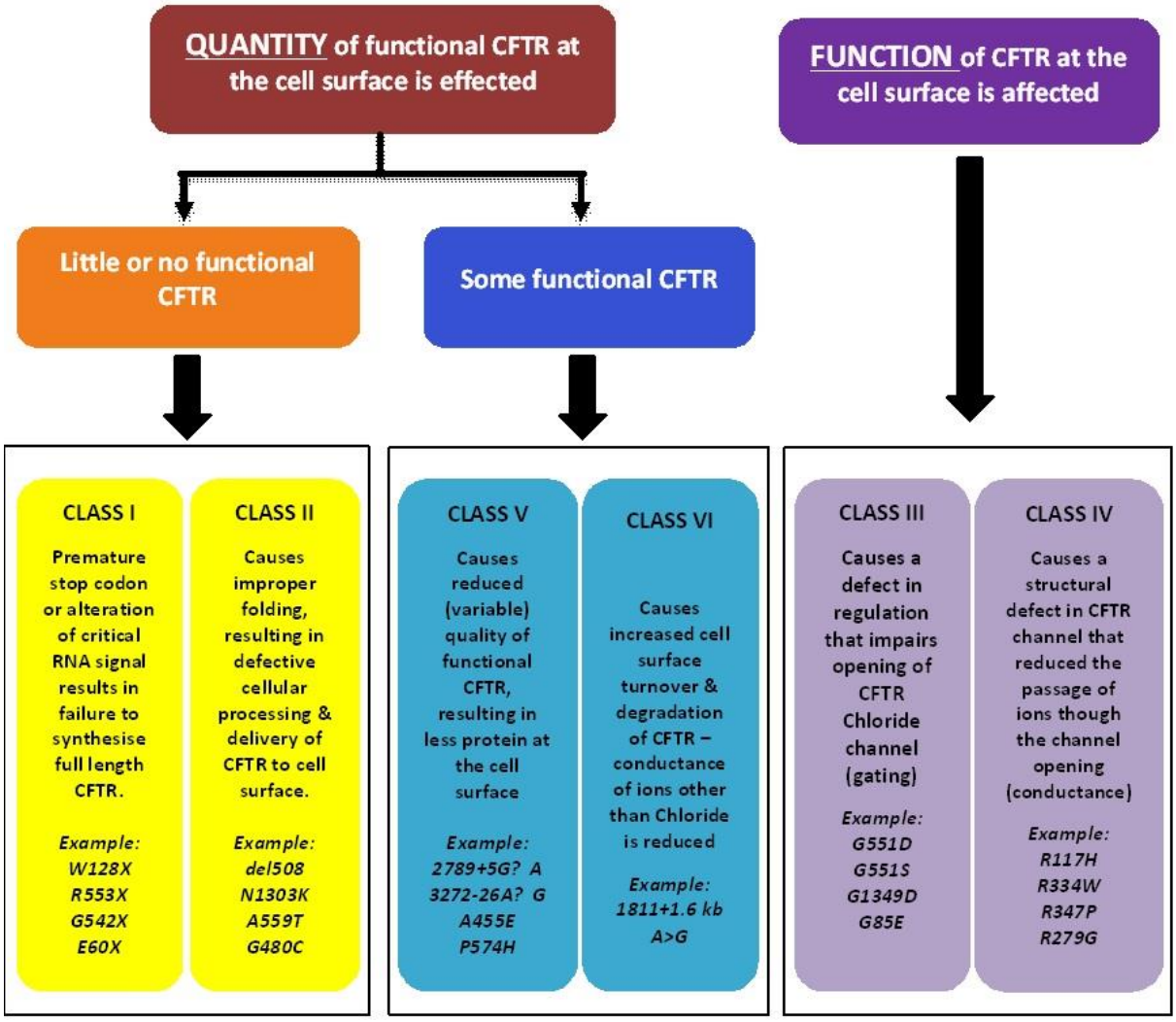

Figure 3.1: Six different classes of CFTR mutation

An accepted molecular classification strategy which organises CFTR variants by their effect on CFTR function. Class I-III variants cause severe dysfunction, and Class IV-V cause reduced or altered function. Class IV-V variants have mild-variable effects on the pancreas and other organs, often leaving sufficient function for basic physiological needs but not enough to handle stress (101). Class I-III are associated with normal or classic cystic fibrosis. Class IV-VI are associated with non-classical or atypical cystic fibrosis.

(Figure adapted from (251)).

3.5.5. Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations and chronic pancreatitis

Specific *CFTR* genotypes are significantly associated with pancreatitis; - patients with genotypes associated with mild phenotypic effects have a greater risk of developing pancreatitis than those with genotypes associated with moderate-severe phenotypes (246). As mentioned previously, two landmark studies demonstrated that severe *CFTR* variants were seen in patients with idiopathic and alcohol associated chronic pancreatitis patients without lung disease (103, 104). However, it was unclear if these patients suffered from mild or atypical cystic fibrosis, or a more complex *CFTR*-mediated pancreatic syndrome (101, 252). It is apparent that effective *CFTR* activity is required for normal duct cell function, and variants in *CFTR* which result in cell dysfunction are associated with susceptibility to pancreatitis (101). Studies demonstrating frequency of *CFTR* mutations (such as F508del) in chronic pancreatitis patients (103, 104), provide evidence that carrier status of well-known cystic fibrosis causing mutations significantly increases risk of pancreatitis. There are also 'mild' mutations which result in the retention of some residual *CFTR* function and can cause atypical cystic fibrosis-like phenotypes (Figure 3.1). Patients with congenital bilateral absence of the *vas deferens* (CBAVD) frequently carry *CFTR* mutations in the absence of classical disease phenotype. This provides evidence that different types of *CFTR* mutations are responsible for different degrees of impairment, which can be associated with diverse clinical disease presentation.

Pathogenic variants in the *CFTR* protein are associated with acute and chronic pancreatitis (235). The *CFTR* is an anion channel that allows the movement of either chloride or bicarbonate across the apical (luminal) membrane from inside the duct cell into the duct, in which it is responsible for increasing pH, as well as initiating and driving pancreatic juice flow (219). Osmotic balance is maintained by regulating the chloride concentration in the cell, and the absorption of sodium ions into the cell. The

primary function of the duct cell is to secrete bicarbonate-rich fluid, which flushes zymogens from the pancreas into the duodenum, - and *CFTR* is the most important molecule for fluid secretion in the pancreatic duct cell. Mutations in *CFTR* which cause dysfunction may result in the inability to flush zymogens from the duct. When retained in the duct, zymogens may become active, begin to digest the surrounding pancreas, and this may lead to acute pancreatitis (235). Initially chloride (Cl) – conductance in sweat ducts was discovered to be impaired in cystic fibrosis, a finding which is now known to extend to all *CFTR*-expressing cells (pancreas, intestine, male reproductive gland, nasal canal). The identification of additional cystic fibrosis causing mutations bearing normal chloride channel activity indicated that other *CFTR*-dependent processes contribute to the disease. Indeed, *CFTR* is known to regulate other transporters chloride coupled bicarbonate transport. Recent data suggest that *CFTR* pathogenic variants that affect bicarbonate conductance, (while maintaining chloride conductance), have a major effect on the pancreas, but minimal effect on the lungs, since the pancreas uses *CFTR* as a bicarbonate channel (224). There are also sensors inside the duct cells that change the permeability of *CFTR* to promote conductance of bicarbonate when intracellular concentrations are low (253). The bicarbonate secreted from pancreatic duct cells provides an optimum pH environment for digestive enzymes in the duodenum and neutralises gastric acid. Bicarbonate is also responsible for the solubilisation of macromolecules to prevent aggregation of digestive enzymes and mucins (254, 255). In line with this notion, abnormal bicarbonate secretion is therefore associated with pancreatic diseases such as cystic fibrosis and chronic pancreatitis (103, 256).

A number of studies have described *CFTR* mutations (commonly F508del) amongst chronic pancreatitis patients which provide evidence that carrier status of well-known cystic fibrosis mutations significantly increases pancreatitis risk (104, 219, 257). However, the functional effect of rare (or atypical) *CFTR* variants is not easily

discernible. A recent study from the North American Pancreatitis Study 2 (NAPS2) consortium demonstrated that *CFTR* R75Q variant increases the risk for chronic pancreatitis, but does not increase risk for the development of lung disease (224). This study identified both F508del and R75Q as the most frequent variants over-represented in familial and non-alcohol pancreatitis patients (224). Further, functional studies also demonstrated that the *CFTR* R75Q variant specifically disrupted the bicarbonate but not the chloride secretion (219, 224). The implication of this finding is that pancreatic duct secretion is markedly altered (because neither chloride or bicarbonate can be transported across epithelial cells) and the critical level of bicarbonate secretion which protects the pancreas is lost (219). These findings infer that there may be an entire class of *CFTR* variants (previously assumed to be benign as they do not cause classic cystic fibrosis) that result in chronic pancreatitis (219).

3.5.6. Chymotrypsin C (CTRC) and Calcium sensing receptor (CaSR) mutations and chronic pancreatitis

Biomolecular processes and extensive genotyping of relatively unexplored genetic regions has led to the discovery of additional genes which are involved in the pathogenesis of chronic pancreatitis. Because trypsin degradation serves as a protective mechanism against pancreatitis, it was hypothesised that loss of function in trypsin-degrading enzymes would increase the risk of pancreatitis (106). *CTRC* is thought to degrade all human trypsin and trypsinogen forms with high specificity and is therefore considered a pancreatitis-associated gene (258). Rosendahl and colleagues (106), using a large European cohort, discovered that two *CTRC* variants were significantly overrepresented in chronic patients compared to controls. Multiple *CTRC* variants have been reported in studies from other regions of the world (105, 259, 260) and, although the mechanisms by which *CTRC* protects against pancreatitis have been

established, the importance of *CTRC* variants in terms of the risk for recurrent acute and chronic pancreatitis are unclear (101)

CASR is a protein-coupled receptor that plays a key role in calcium homeostasis. It does so by sensing extracellular calcium levels and is expressed in the parathyroid, bone, intestine, kidney, brain, and in both acinar and duct cells of the pancreas (219, 232). Experimental evidence has linked elevated acinar cell calcium levels with acute pancreatitis in association with premature activation of trypsinogen to trypsin (261, 262). From this it was proposed that mutations in *CASR* may lead to increased susceptibility to chronic pancreatitis.

In 2003, a German study reported on a family with familial hypercalciuric hypercalcaemia and chronic pancreatitis (263). The authors found that while family members with an isolated *CASR* mutation remained healthy, those with a combination of *CASR* and *SPINK1* (N34S) mutations caused chronic pancreatitis (263). A larger study of 19 families with idiopathic chronic pancreatitis again found that only those with a combination of *CASR* and *SPINK1* (N34S) mutation developed pancreatitis, whereas in healthy subjects only an isolated *CASR* or *SPINK1* gene mutation was detected (264) This indicates that *CASR* has a modifying role in the aetiology of chronic pancreatitis. Another study of 338 chronic pancreatitis patients in the US again found that the *CASR* variant R990G is a significant risk factor for chronic pancreatitis, and a threefold increased risk was observed in patients who reported moderate or heavy drinking (262). However, in this study there was no association found between *CASR* and *SPINK1* (N34S). The authors postulated that *CASR* polymorphisms are relatively small and become clinically significant in the presence of additional risk factors in an additive or multiplicative way (262)

Unlike *CFTR* and *SPINK1* mutations, homozygous (two of the same allele) or compound heterozygous (two different mutant alleles) mutations in *CTRC* and *CASR*

have not been found in familial or sporadic chronic pancreatitis, indicating that independently they are not sufficient to cause recurrent acute and chronic pancreatitis, and almost always occur with heterozygous variants in *PRSS1*, *CFTR*, *SPINK1* (101, 219, 226, 259). Again, this emphasises that combinations of genetic factors are required to increase risk for recurrent acute and chronic pancreatitis (101).

3.5.7. Idiopathic chronic pancreatitis genetic associations

Owing to the large proportion of patients with unknown cause (idiopathic) chronic pancreatitis, genetic susceptibility to disease is of particular interest in these patients. While homozygous mutations of *PRSS1* are normally associated with hereditary pancreatitis (51), 15% to 40% of patients with idiopathic chronic pancreatitis are known to carry certain mutations of the *SPINK1* gene on one or both alleles (71). The frequency of *CFTR* mutations is considerably more than expected in idiopathic chronic pancreatitis patients (104, 265). Two landmark studies (103, 104) identified severe CFTR mutations in idiopathic chronic pancreatitis patients, without lung disease, results of which have since been replicated. Two more recent studies analysed the complete *CFTR* coding sequence, along with *SPINK1* and *PRSS1*, in idiopathic chronic pancreatitis patients (225, 252). In both studies, 25% and 30% of patients carried at least one *CFTR* mutation or were compound heterozygous for a *CFTR* mutation (225, 252) Further, patients were also found to be trans-heterozygous (heterozygous at two different genes) for a *CFTR* and *SPINK1* mutation (225, 252). In general it is believed that idiopathic chronic pancreatitis patients have one classic cystic fibrosis mutation, and a second mutation which is presumably insufficient to produce cystic fibrosis in homozygous form (265). These data have led to the hypothesis that idiopathic chronic pancreatitis may actually represent ‘atypical cystic fibrosis’ (85). However, since several patients were trans-heterozygous for *CFTR* alteration, and *PRSS1* or *SPINK1*

variant, combinations of mutations in different genes appear to be relevant for disease pathogenesis (71, 85).

3.5.8. Alcohol–induced chronic pancreatitis genetic associations

It is firmly established that the pancreas metabolises alcohol to its toxic metabolites acetaldehyde and fatty acid ethylesters (229). By-products of ethanol metabolism are known as reactive oxygen species, which can induce oxidative stress within the pancreatic gland (266). There is also significant knowledge to support the deleterious effect of alcohol and its metabolites on acinar cell organelles, and signalling pathways, which predispose the cell to premature intracellular digestive enzyme activation by lysosomal enzymes (229). Alcohol and its metabolites have been shown to destabilise lysosomes (containing lysosomal enzymes) and zymogen granules (containing digestive enzymes) (266-268). This effect is mediated by oxidant stress, cholesterylesters and fatty acid ethylesters, which increase digestive and lysosomal enzyme content due to increased synthesis and impaired secretion of these enzymes (268-272). These changes are thought to sensitise the exocrine cells so that in the presence of an appropriate trigger or co-factor, overt cell necrosis is initiated (229). Repeat episodes of acute alcohol-induced pancreatic injury are known to cause residual damage to the pancreas gland. This eventually results in atrophy and fibrotic changes (229).

An association between alcohol consumption and pancreatic diseases has been recognised for decades, but epidemiological studies have shown the absolute risk for individuals who drink alcohol is actually low (230). Fewer than 5% of heavy alcohol users ultimately develop chronic pancreatitis (95, 273). In fact, the risk of alcoholic pancreatitis when adjusted for smoking in regression analysis is low (94). The role of alcohol attributed to pancreatitis cases varies in studies worldwide, which might be

associated with the use of different classification criteria, as well as the differences in the various populations studied. A genetic risk for alcohol-associated chronic pancreatitis on the X-chromosome Claudin 2 locus (*CLDN2*) had been reported by Whitcomb and colleagues (274). The *CLDN2* locus minor allele on the X-chromosome includes non-protein coding variants that increase the progression from acute to chronic pancreatitis. The homozygous (hemizygous in males) *CLDN2* genotype confers the greatest risk, and its alleles interact with alcohol consumption to amplify risk (274). This may partially explain why men more commonly have alcohol-associated chronic pancreatitis compared to women. In terms of early clinical intervention, genetic testing for the X-chromosome factor for moderate alcohol consumers with pancreatitis-like pain could provide an early warning. These data indicate that alcohol may be a weak susceptibility factor (first hit, SAPE hypothesis, see Figure 1.7), but a strong modifier factor (second hit), being especially potent when there is concurrent smoking (94) and *CLDN* risk variant (101, 274).

3.6. Conclusion

This chapter detailed four key themes of chronic pancreatitis management which are identified and known as being critical research gaps. Research into these specific areas of chronic pancreatitis aims to improve understanding, add to the existing literature, provide direction in future research and ultimately enhances patient care.

Chapter 4 which follows describes the general methodologies which underpin this thesis and the research studies outlined in chapters 5-8.

4. Chapter 4 – General methodology

This chapter details the methodologies used throughout the research studies, including details on the role of the author as lead investigator, the study aims and objectives, acquisition of ethical approval, study design, setting, recruitment, patient and doctor assessments, and statistical analyses. Specific additional details pertaining to individual studies are provided in the relevant chapters, where appropriate.

4.1. Investigator and data collection

The author conducted all aspects of the research throughout this thesis including literature reviews, study design, data collection, data entry, statistical analysis, and writing of research papers, conference abstracts, and the final thesis. Some aspects of the research required assistance of clinical nurse specialists, librarians, statisticians, and specialists, detailed below:

- Dr Brendan O'Shea, GP and head of GP training in Ireland, provided guidance on the development of the survey for GPs in Part B of Chapter 5. Dr O'Shea also supervised and collaborated in the development of the General Practice guidelines for chronic pancreatitis, in Part C of Chapter 5
- Mr Dara Kavanagh, Consultant Surgeon, assisted with the design and development of the specialist survey in Part A of Chapter 5
- The Health Pricing office provided data and guidance in Chapter 6
- Health Atlas Ireland, provided access to the HIPE database, in particular Ian Folan, Fionnuala Donohue, and Anne O' Farrell
- Mr Paul Haughton, HIPE Department, Tallaght University Hospital, provided advice and assistance in the acquisition and analysis of data for Chapter 6

- Mr David McNaughton, Medical Librarian at the University of Ireland, Trinity College Dublin provided assistance with the systematic review in Chapter 6
- Dr Barbara Ryan, Consultant Gastroenterologist assisted with the design and interpretation of the data in the study in Chapter 8, and also in the dissemination of the specialist survey in Part A of Chapter 5
- Ms Marie Egan, Clinical Nurse Specialist Pancreas and Biliary Diseases, assisted with the identification of suitable patients and with patient recruitment for studies in Chapters 7 and 8
- Mr Mark Dobson, GI Laboratory technician, provided guidance with the clinical aspect of the study in Chapter 8. Provided training and assistance with undertaking the breath testing
- Professor Ross McManus, Professor of Molecular Medicine, was a collaborator for the study in Chapter 8, specifically assisting with the study design, the technical aspects of the analysis, and in the interpretation of data
- Dr Joe McPartlin, and Ms Mary Cuneen, Institute of Molecular Medicine, St James's Hospital, provided assistance and technical expertise regarding the extraction of DNA and variant sequencing in Chapter 8
- Phlebotomy was undertaken by trained Phlebotomists from the Phlebotomy Departments of Tallaght University Hospital and St James's Hospital for Chapter 8

4.2. Ethical approval

4.2.1. Informed consent

Prior to undertaking this research, ethical approval was sought from the Tallaght University Hospital and St James's Hospital Joint Research Ethics Committee (JREC) and the St Vincent's University Hospital Research Ethics Committee. Letters of ethical approval are included in Appendix B. Prior to inclusion in each of the research studies,

patients were provided with patient information leaflets detailing the studies in full, and given the opportunity to consider and ask any questions prior to deciding to be included. Patients were asked to keep the patient information leaflets and supplied with relevant contact details enabling them to contact the investigator. Prior to inclusion, written signed informed consent forms were obtained from all cases and controls in the recruitment studies. Patients were made aware that their participation was entirely voluntary, that they may choose not to take part, and that they may remove themselves at any time during the study, without prejudice or discrimination (and that this would in no way influence their medical care).

4.2.2. Data Storage

Confidential patient information pertaining to the studies was stored in a locked filing cabinet within the Trinity Centre for Health Sciences (research offices) to which only the author and those directly involved in the studies had access. Data analysis was conducted in the Trinity Centre for Health Sciences, located in Tallaght University hospital. Electronic information was stored on a confidential password protected computer. Care was taken not to disclose any information that could identify or connect any of the participants to the study. On completion of data analysis, computerised information was transferred to a password protected CD and stored in a locked filing cabinet. Access to the Trinity Centre for Health Sciences is by personalised swipe card, and the research offices require a key for access. All data were treated as confidential and never disclosed to a third party.

4.2.3. Vulnerable subjects

The study included only adults above 18 years of age. Intellectually impaired adults, people with brain injuries, or otherwise incapacitated were not included, due to risk of lack of comprehension of the study or inability to provide informed consent. Women of

child bearing age were not excluded, but those who were pregnant at the time of the study were not included. Elderly / aged persons >65 years were not excluded, as chronic pancreatitis is a disease that may affect this age group. Elderly patients (or patients of any age) who were vulnerable were not included. Any person who was unable to provide informed written consent or who did not willingly volunteer for inclusion in the studies was not included. Where Tallaght University Hospital staff members were recruited as controls, participation was entirely voluntary, and first contact was made by the subject by means of phone call or email in response to study advertisements.

4.2.4. Study sponsorship

The studies outlined in this thesis were part-funded by the Department of Surgery, Trinity College Dublin, and by Mylan Pharmaceuticals (by means of an education grant). No constraints were exerted on any of the studies. Mylan were not involved in study design, advertisement, recruitment, analysis, commentary, or in the write-up of any of the manuscripts for publication. Neither the author nor any other investigator involved in the studies had any conflicts of interest.

4.3. Study design

To fulfil the aims of this thesis, several methodological and scientific approaches were adopted, and specific details pertaining to each study methodology are detailed in the relevant study chapters (chapters 5-8). The research studies were conducted between September 2014 and January 2018.

4.3.1. Study setting

Tallaght University Hospital (formerly the Adelaide and Meath National Children's Hospital AMNCH), is a tertiary referral centre for pancreatic diseases in Ireland and

therefore patients recruited to the studies were from all parts of Ireland. Patient-related studies took place within Tallaght University Hospital, and all patients were recruited from within specialist pancreatic clinics within the hospital or the pancreatic database held in the Centre for Pancreatico-bilary diseases in the hospital, with the exception of the genetic study (Chapter 9), where patients were also recruited from both St Vincent's University Hospital, and St James's Hospital. The Centre for Pancreatico-Bilaty diseases in Tallaght University Hospital is thought to treat up to 200 patients per year.

4.3.2. Study recruitment

Patients and study respondents were recruited to the study utilising the following approaches:

1. Patients attended outpatient appointments at specialist pancreatic clinics, where they were informed and invited to partake in the study
2. Patients were referred to the specialist pancreatic team for inclusion in the study by other medical or surgical specialities within the hospital or in St Vincent's University Hospital / St James's Hospital
3. Patients with prior admissions to Tallaght University Hospital with a diagnosis of chronic pancreatitis were identified from the existing departmental pancreatic database (managed by a database co-ordinator), and were approached by letter or phone call to participate.
4. Patients were referred for inclusion in studies by consultants from other hospitals who were aware of studies and their patients were interested in participating
5. Healthy controls were recruited through study advertisement using a control recruitment poster which was available in public areas in Tallaght University

Hospital. Controls were also recruited through email advertisements to local businesses, factories and taxi services

6. Specialist, consultants and GPs were included in the studies as clinical respondents following email or written invitation to participate

4.3.3. Questionnaires

Questionnaires, data collection forms, and assessment forms were utilised for all recruitment studies, and are discussed within each individual study chapter. All such documentation is included in the Appendices.

4.3.4. Assessment and equipment

General assessment techniques, methods and equipment used during the studies are detailed here. Specific parameters, reference ranges, and technical information are detailed within each individual chapter as appropriate.

4.3.5. Biochemistry

Blood samples for the genetic study were taken in the Phlebotomy Department in Tallaght University Hospital and were processed according to standard protocols in Tallaght University Hospital Biochemistry Department. Blood samples were extracted in to standard ethylene diamine tetra-acetic acid (EDTA) tubes, and were frozen stored in -80 degree Celsius in the laboratory prior to transport to the Institute of Molecular Medicine, St James's Hospital for subsequent DNA extraction and genetic testing. Details of the specific gene variant assays and reference ranges are detailed in Chapter 8.

4.3.6. Blood sample transport

Blood samples were transported between Tallaght University Hospital and St James's Hospital by Biomnis™ who are specialists in the safe transport of biochemical samples, and who transported the frozen samples in accordance with standard protocols.

4.3.7. Faecal stool samples

Patients attending the specialist pancreatic clinics for the treatment of chronic pancreatitis in Tallaght University Hospital were asked to provide a stool sample to assess pancreatic function as standard procedure. Stool samples for faecal-elastase-1 were sent to the Biochemistry Department of Tallaght University Hospital for sample preparation. Samples were then outsourced and shipped to The University Hospital of South Manchester (UK) for faecal-elastase-1 analysis using assays linked to immunosorbent assay (ScheBo® Pancreatic Elastase-1 Stool Test, Germany), expressed as ųg / g stool (see chapter 7).

Table 4.1 details faecal elastase-1 reference ranges.

Result, ug Elastase / g stool (all ages)	**Interpretation**
>200	Normal
100-200	Slight to moderate pancreatic exocrine insufficiency
<100	Severe pancreatic exocrine insufficiency

4.1: Reference ranges for Faecal Elastase-1 (FE-1) test

4.3.8. Glucose hydrogen breath test

To evaluate the presence of small intestinal bacterial overgrowth, patients were required to undergo a fasting glucose hydrogen breath test. The study protocol is

described in detail in Chapter 7. The breath test was conducted using a portable hand-held breath analyser (LactoFAN H_2 Fischer Analysen Instrumente, Leipzig, Germany). This device measures expired hydrogen in parts per million (PPM) from a single breath manoeuvre, and it was calibrated at the appropriate intervals as per company protocol and standards.

Figure 4.1: LactoFAN H2 breath analyser

Figure 4.2: Hydrogen breath test. Photograph showing the use of the hand-held breath analyser

4.3.9. Assessment and classification of chronic pancreatitis disease severity

Patients with a diagnosis of chronic pancreatitis were included in the studies. The diagnosis of chronic pancreatitis was based on typical clinical, imaging, and endoscopic features, and functional tests confirming disease presence. Chronic pancreatitis was diagnosed on the basis of at least two of the following criteria; patient history (abdominal pain typical of pancreatitis), functional deficits (such as endocrine, exocrine deficiency), and/or findings on imaging studies (computed tomography and/or endoscopic ultrasonography). Severity was classified according to the Cambridge classification (Table 4.2) and the TIGAR-O / M-ANNHEIM classification (Table 4.4). The diagnosis of chronic pancreatitis is based on the Cambridge Classification (Table 4.2) and diagnosis criteria from the American Pancreatic Association (Table 4.3) and these are recognised tools for the assessment of chronic pancreatitis.

For Chapter 7 and 8, only patients with idiopathic or alcohol-induced aetiology were included. In all cases disease aetiology was determined and documented by the multidisciplinary clinical pancreatic team. Alcohol-induced chronic pancreatitis aetiology was recorded where alcohol intake exceeds recommended intakes, and in the absence of other causes of chronic pancreatitis. Idiopathic chronic pancreatitis cause is recorded in the absence of other known chronic pancreatitis causes.

Score 1 (Cambridge class 0) • Severity: normal • High quality CT / ERCP /US with whole gland visualisation, with no abnormal findings
Score 2 (Cambridge Class O) • Severity: equivocal • ERCP – less than 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 1) • Severity: mild • ERCP: 3 or more abnormal branches • US/CT: 2 or more abnormal signs: cavities <1 0mm, 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 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) - Gross gland enlargement (> 2 times normal) - Intraductal filling defects or calculi - Duct obstruction, stricture, duct dilation or gross irregularity - 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 cholangio pancreatography *US – Ultrasound *CT – Computed tomography

Table 4.2: The Cambridge classification of disease severity in chronic pancreatitis

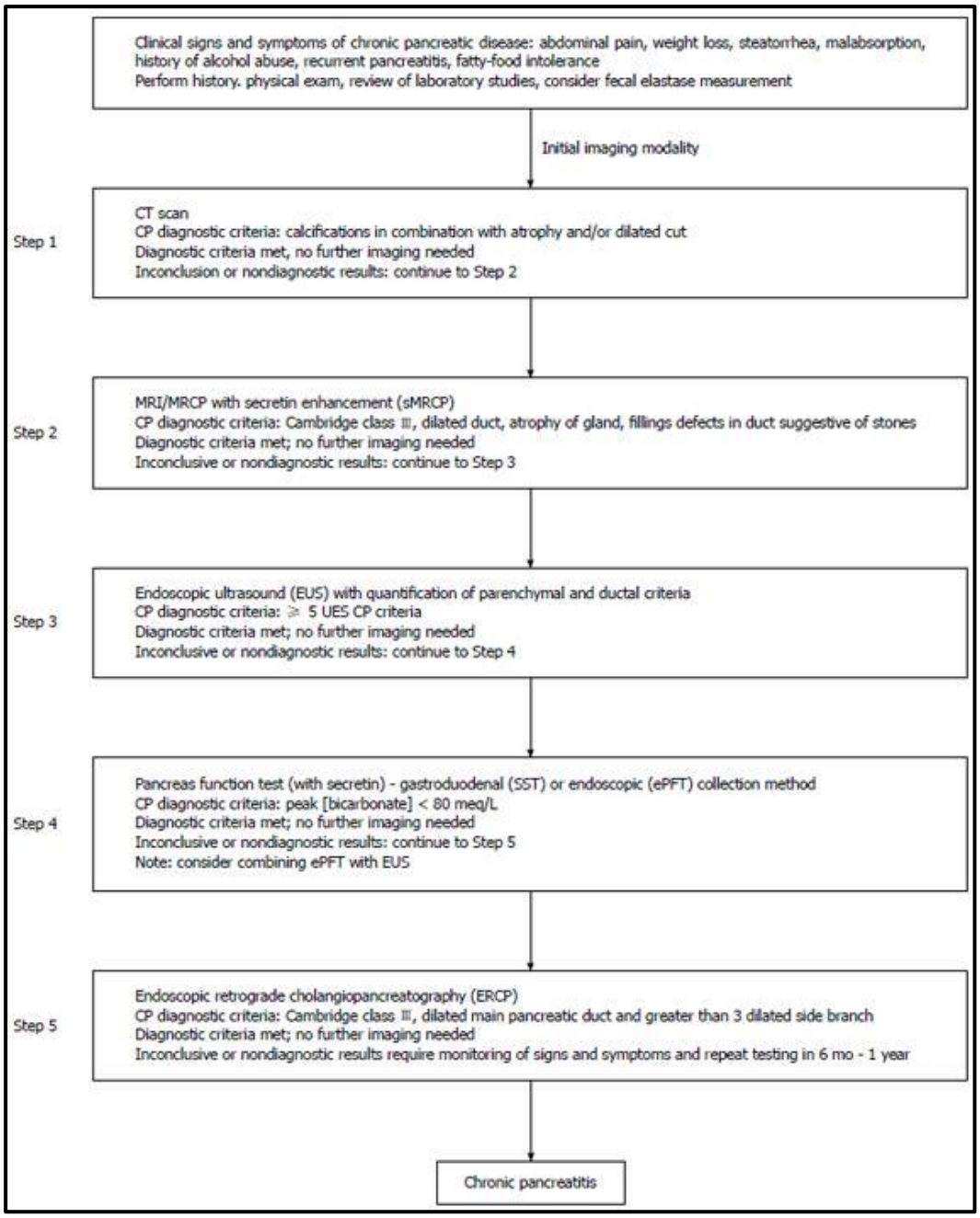

Table 4.3: American pancreatic association stepwise approach to the diagnosis of chronic pancreatitis

Step 1: Survey data review, risk factors, CT imaging. Step 2: Tomography – pancreas protocol CT scan. Step 3: Endoscopic – EUS (standard criteria). Step 4: Pancreas function – dreilling, ePFT (endoscopic pancreatic function test). Step 5: ERCP (with intent for therapeutic intervention) (122)

Classification of chronic pancreatitis aetiology
TIGAR-O
Toxic – metabolic: Alcohol, tobacco smoking, hypercalcemia, hyperlipidemia, chronic renal failure, medications, toxins
Idiopathic: early-onset, late-onset, tropical
Genetic mutations: PRSS1, CFTR, SPINK1, other
Autoimmune: isolated syndrome
Recurrent and severe acute pancreatitis associated with chronic pancreatitis: Post necrotic, (severe acute pancreatitis), vascular disease/ischaemia, post-irradiation
Obstructive: Pancreas divisum, sphincter of Oddi disorders, duct obstruction (eg. Tumor), post traumatic pancreatic duct scars
M-ANNHEIM
M – multiple risk factors including;
Alcohol consumption: Excessive (>80 g/d), increased (20-80 g/d), moderate (<20 g/d)
Nicotine consumption
Nutritional factors: High calorie proportion of fat and protein, hyperlipidemia
Hereditary factors: Hereditary , familial, idiopathic (early-onset, late-onset), tropical
Efferent duct factors: pancreas divisum, annular pancreas and other congenital abnormalities of the pancreas, pancreas duct obstruction (eg tumor)
Immunological factors: Autoimmune pancreatitis
Miscellaneous and rare metabolic disorders: Hypercalcemia, hyperparathyroidism, chronic renal failure, drugs, toxins

Table 4.4: Classification of chronic pancreatitis disease aetiology

TIGAR-O (63) and M-ANNHEIM (80)

4.4. Follow-up of patients post study

For Chapter 7 SIBO, patients were given their results (positive/negative) on the day of testing, and a letter describing the findings was sent to their consultant (for medical record filling). Following consent from each patient, a copy of the results was sent to the general practitioner for follow-up as appropriate, and contact details were provided for the GP to contact the team if required Patients who were positive for bacterial overgrowth were treated with antibiotic therapy (prescriptions were provided on the day of testing), as per the pancreatic team protocol. They were then followed up in the specialist pancreatic clinics, and retested if required. Patients who tested positive for SIBO received a follow-up phone call to ascertain symptom improvement. No patient required retesting at the time of writing.

For Chapter 8 (genetic study), results were sent to patients, and to their consultant. Where a positive mutation was found in patients in the genetic study, patients were reviewed in the specialist pancreatic clinics, and further referred to the National Centre for Medical Genetics in Our Lady of Lourdes Hospital, Dublin for further assessment as appropriate. The decision to refer for further assessment was decided by the specialist pancreatic team.

4.5. Copyright and permissions

All published works which are quoted throughout this thesis are appropriately referenced. Where tables, figures or illustrations are replicated, or where the author's own work from a scientific journal is included, relevant licence agreements for copyrighted material was obtained through Rightslink®, and where necessary, permission was sought from the authors directly.

4.6. Statistical analysis

The thesis author conducted the statistical analysis for the studies, with assistance and guidance from the research supervisors where necessary.

The statistical software package used was the Statistical Package for Social Sciences (SPSS Version 22, Chicago, IL, USA, 2015) and thematic content analysis was used for qualitative information. Data analysis was conducted on Trinity College Dublin on a Dell personal computer using the institutional licenced software access. Specific analyses techniques employed in the studies are detailed in their relevant chapters. In all cases, unless otherwise specified, a P value of <0.05 was deemed to be statistically significant.

5. Chapter 5 - Chronic pancreatitis in primary and hospital-based care in Ireland

This chapter describes a study of three parts.

Part A and **B** of this chapter describe two studies examining the primary and hospital-based management of chronic pancreatitis in Ireland. These studies were cross-sectional, using two descriptive surveys. Specifically, current practice in chronic pancreatitis was explored, as well as practice demographics, access to specialist services, patient numbers, awareness of guidelines, and perceptions about the need for a national disease registry for disease surveillance.

Part C of this chapter describes the design, development, and publication of guidelines for the management of chronic pancreatitis in primary care in Ireland. Results from the studies described in Part A indicated a lack of knowledge of Irish GPs on the management of chronic pancreatitis. To improve care of patients in primary care the thesis author, in collaboration with the Irish College of General Practitioners (ICGP), devised Quick-Reference Primary Care guidelines (124).

5.1. General introduction

Chronic pancreatitis has significant healthcare and socioeconomic requirements for patients and for the healthcare system. Chronic diseases, in general, result in a decreased quality of life, increased morbidity, higher mortality, and constitute a significant healthcare resource burden (148). Chronic diseases constitute a sizeable percentage of healthcare service activity and budgetary expenditure in Ireland (3), and a similar effect is seen in other countries. The number of patients with chronic conditions is estimated to substantially increase in Ireland between 2007 and 2020, with the number of adults affected by chronic conditions expected to increase by approximately 40% (154). Due to an aging population, many patients have multiple chronic diseases for many years requiring treatment across many healthcare settings. This results in a considerable resource burden at both primary care and hospital level. For chronic pancreatitis in particular, there are many reasons for inflated healthcare cost; recurrent hospitalisation, repeated primary care visits, ongoing management of exocrine and endocrine impairment, malnutrition, chronic pain treatment, management of multiple morbidities, and associated disease complications. Several studies have described the socioeconomic implications of chronic pancreatitis. Issues of concern include difficulty in maintaining employment (275) reduced quality of life (correlated with pain scores) (276) and lengthy hospital stays (277). In a study of health-related quality of life in patients with chronic pancreatitis, patients reported having substantial financial complications compared to healthy controls (278). Duggan (114) reported that a third of patients (35.5%) were unemployed as a direct consequence of chronic pancreatitis, while just over half were working in either full- or part-time employment compared to 97% of age- and sex-matched controls.

As a progressive, incurable disease, the aim of medical treatment is to manage adverse symptoms and associated complications to reduce overall impact of the disease. A number of studies worldwide have focussed on different epidemiological,

aetiological and surgical aspects of chronic pancreatitis. There are studies available on areas such as diagnosis, treatment, disease cost, associated disease complications, and quality of life. However, the management of chronic pancreatitis is frequently different between countries and healthcare jurisdictions. In particular, there has been little published on the management of chronic pancreatitis patients in primary care. Over the last decade, a number of guidelines have been published providing guidance on hospital-based management of chronic pancreatitis (117, 118, 120-123, 175, 279). However, little or no emphasis has been placed on chronic pancreatitis management outside of the acute setting. Furthermore, there has been little investigation into guideline adherence, patient care, or factors which could help improve disease management.

5.1.1. Primary care management of chronic pancreatitis

In recent years there has been a growing momentum for the relocation of chronic disease care from secondary to primary care in Ireland. This has been emphasised in a national framework policy by the Irish government (280), and GPs have an important role in this transition. Due to the nature of chronic pancreatitis as a complex disease (with chronic pain, endocrine and exocrine impairment, malnutrition, multi-morbidities, disease-related complications and socioeconomic factors) GPs have an important role in its management. As well as managing pain, endocrine and exocrine insufficiency, - GPs are gatekeepers to secondary and tertiary care, as well as coordinating care. They determine requirement for hospital-based care, coordinating the discharge of hospitalised patients, providing a conduit between hospital and home, as well as integrating care within the primary care team. It is important that GPs are aware of the risk factors and potential signs and symptoms for early chronic pancreatitis, as expedited diagnosis could improve outcomes by the institution of early therapeutic interventions

5.1.2. Hospital-based management

Due to the complex nature of the disease, hospital-based care is best managed by a dedicated multidisciplinary team. Specifically, optimal management of chronic pancreatitis requires a multidisciplinary team of gastroenterologists and/or surgeons, radiology, endocrinology, pain management, clinical nutrition, specialist nurses, psychology, and medical social work (64, 281). The management principles of chronic pancreatitis include the education and reinforcement of lifestyle changes (such as smoking and alcohol cessation), dietary intervention, PERT, managing adverse symptoms, and a stepwise approach to analgesia (282) and planning for end-of-life care. Patients with ongoing symptoms may require endoscopic intervention, radiological intervention, and/or surgery. As a chronic condition, long-term follow-up is important. Post diagnosis follow-up studies including history, physical examination, clinical findings, transabdominal ultrasound, and laboratory testing, such as HbA1c should be completed annually (123, 175). The screening of high-risk groups of chronic pancreatitis (including smokers and carriers of *PRSS1* mutations) at regular intervals for the development of pancreatic carcinoma is beneficial, however the length of examination intervals has not yet been reliably established and surveillance algorithms are not currently available (123). According to recently published German guidelines for chronic pancreatitis management, clinicians should not wait for warning signs before following-up patients, as many relevant complications of chronic pancreatitis have already caused irreversible organ damage once warning signs appear (123). Good chronic care incorporating The Chronic Care Model (www.improvingchroniccare.com), should include consultation with patients regarding their goals and objectives, provision of appropriate and high quality information regarding their care, and implementing good care coordination, particularly during care transitions (283). An important facet of the Chronic Care model is patient self-management in chronic disease. This involves patient-professional partnership, collaborative care and self-management education to

support patients to achieve the best quality of life with their chronic disease (172, 284) and this is a crucial aspect of the management of chronic pancreatitis patients.

5.1.3. Standards and guidelines for chronic pancreatitis

The last number of years has seen a number of publications on the management of chronic pancreatitis. Despite this, some basic controversies exist regarding the management of chronic pancreatitis which is a rate limiting factor in the delivery of appropriate care, especially in the primary care setting. Over the last decade there have been at least seven publications on the management of chronic pancreatitis from Europe (117, 118, 120, 121, 123, 175, 279) and at least one publication from the US (122). The majority of these guidance documents focus on diagnosis (117, 118, 122, 123, 279), treatment (117, 118, 120, 123, 175), surgery (123, 175, 279), interventional endoscopy (123, 175), or management of symptoms and complications (117, 120, 121, 123, 175). To the author's knowledge, no guidance document has been published instructing the care of the chronic pancreatitis patient outside of the acute hospital setting, despite many publications advocating the need for long-term management of patients to take place in the primary care setting. This constitutes a critical gap in the guidelines.

5.1.4. Study rationale

There is a dearth of information available on the management of chronic pancreatitis in primary and hospital-based care in Ireland, and worldwide. A study was designed to investigate the knowledge and current practices of clinicians in the management of chronic pancreatitis in hospital and primary care settings. Meeting the complex needs of patients with chronic pancreatitis is an ongoing challenge for all clinicians. Guidelines are a way of supporting clinical practice by describing appropriate care and

reducing variations in practice. Assessing clinical practice in the management of chronic pancreatitis can benchmark care against recommended guidelines to ensure patients are managed efficiently and effectively.

A number of international guidelines have been published on the diagnosis, treatment and management of chronic pancreatitis, focussing predominantly on in-patient care, with aspects of the follow-up care required at specialist pancreatic clinics. The management of chronic pancreatitis had not previously been investigated in Ireland. The existence of guidelines provides no guarantee of implementation or adherence, and assessing disease management is an important aspect of ensuring appropriate care. No guideline exist outlining treatment and management of chronic pancreatitis patients in primary care. These deficits represent distinct research gaps.

Assessing knowledge and current practices can provide the basis for comparison to recommended guidelines. Clinical practices should reflect current best evidence and be concordant with evidence-based recommendations. There is limited knowledge about chronic pancreatitis management in Ireland and examination of management practices reported by clinicians can identify the extent to which management is supported by research and recommended practices. Knowledge of practices may provide opportunities for education and improvement.

5.1.5. Study objectives

The thesis author sought to describe the current management of chronic pancreatitis in both primary and hospital-based care in Ireland. The aims of this study were several fold;

- To provide a baseline assessment of the views of clinicians on the current management of chronic pancreatitis in Ireland
- To identify any perceived barriers to current care provision

- To outline improvements that could potentially positively impact both patient and management of this chronic disease
- To acquire information on patient numbers, demographics, clinician experience, access to specialised care, multidisciplinary team availability, the use of guidelines, the utility of a disease registry, and perceptions on potential improvements in patient care and management.

5.1.6. Ethical considerations

Ethical approval for this study was granted by the Tallaght University Hospital / St James's Hospital Joint Research Ethics Committee (AMNCH / SJH JREC, REF; 2015-03 List 11(2)) (Appendix B). As this study was a descriptive survey examining practice, containing no information related to patients beyond estimations of numbers, and patients were not identifiable, the level of perceived risk or ethical hazard was considered to be low. Permission to send the survey to recipients was granted by chairpersons from Royal College of Surgeons Ireland (RCSI) and the Irish Society of Gastroenterology (ISG).

5.2. PART A – Hospital based survey of specialists

5.2.1. Introduction

There have been little or no studies worldwide analysing the management of chronic pancreatitis from those directly charged with diagnosing and treating patients. Guidelines are available for the management of chronic pancreatitis; however little is known about clinical practice and whether guidelines and recommendations are adopted by Irish consultants. Therefore, this study was designed to investigate

gastroenterologists and specialist's knowledge and current management of chronic pancreatitis at hospital level.

5.2.2. Methods hospital-based survey

5.2.2.1. Hospital-survey

The first survey of hospital-based care targeted gastroenterologists and general surgeons. This survey consisted of 25 questions which was first piloted to a group of n=10 specialists for relevance, purpose, suitability and content analysis. This survey was designed to explore trends in tertiary care in terms of chronic pancreatitis management, demographics, patient numbers, caseload, institution type, education, guidelines, insights and concerns regarding chronic pancreatitis management, acute pancreatitis patient numbers, and opinions on the development of a national chronic pancreatitis disease registry (perceived need, benefits and barriers).

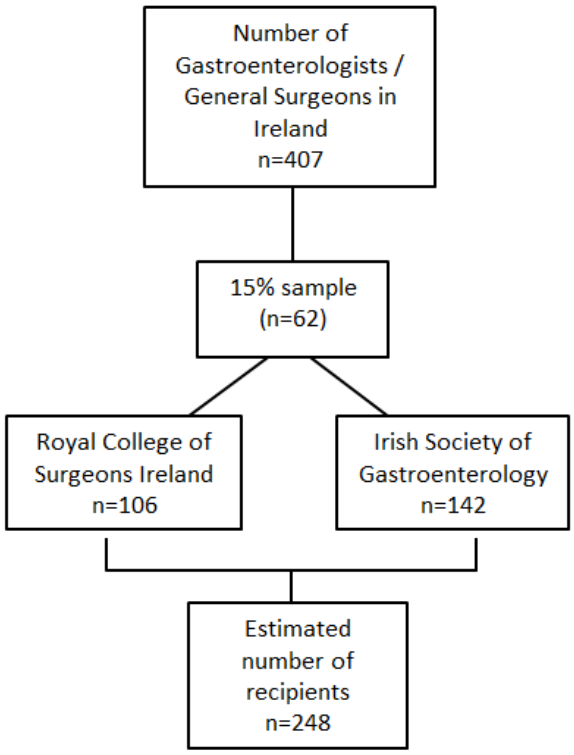

Figure 5.1: Gastroenterologist / general surgeon study flow chart

This figure details the Gastroenterologist and General Surgeon study flow chart. According to the Irish Medical Council, the number of Gastroenterologists and General Surgeons registered in 2014 in Ireland was 407. The bottom 2 boxes demonstrate the (approximate) number of recipients of the survey from RCSI and the ISG.

5.2.2.2. Data collection

The survey was piloted (n=10) to a group of gastroenterologists and general surgeons for usability, content analysis and relevance. Only minor amendments to the survey instrument were made following pilot, and these included changes to question wording and layout or order of questions. It was decided that an online survey would be more suitable for this group of specialists, done *via* the two relevant educational and professional organisations. The survey was emailed to all respondents included on correspondence mailing lists targeted *via* the Irish Society of Gastroenterologists (ISG) and the Royal College of Surgeons Ireland (RCSI). The email included an invitation to

participants to follow a link to complete the online survey *via* the electronic survey software, Survey Monkey©. Following this, two subsequent reminder emails, each one month apart, were sent to all respondents included on the two institution mailing lists. Both emails included the survey link to complete the online survey, and information to contact the research team if needed.

5.2.2.3. Determination of response rate

According to the Irish Medical Council, the total number of gastroenterologists, and general surgeons working in Ireland in 2014 was 407 (285) (Figure 5.1). In some institutions it is possible that several consultants are involved in the care of chronic pancreatitis patients. As the nature of this survey examined practice and management, it was not limited to one group of specialists in one institution. The survey was distributed electronically from confidential internal society and academic institutions which may have included surgeons and doctors of other specialities. Therefore, due to the confidential nature of these internal lists, the precise professional breakdown of recipients is unknown. It is also not possible to determine if the survey was forwarded a number of times, or confirmation of receipt of the survey link. According to the ISG (personal communication) the survey was sent to 345 recipients from their database, which they estimate to include 92 consultant gastroenterologists and 50 surgeons (n=142). The remainder of this list is made up of Specialist Registrars, Registrars, Senior House Officers (SHO), and scientists. According to RCSI the survey was sent to n=106 general surgeons, (an additional 58 surveys were sent to breast and vascular surgeons who are assumed to not manage chronic pancreatitis). Therefore, the estimated number of recipients is n=248. The response rate to the email based survey was 27.4%.

5.2.3. Results: hospital-based survey

5.2.3.1. Gastroenterologist / General Surgeon survey

In total, 68 gastroenterologists and general surgeons completed the online survey. There were 180 who were characterised as incomplete, declined to participate and no response. Therefore, the response rate was 27.4%.

5.2.3.2. Demographics / practice characteristics

Of those that completed the survey, 57.4% (n=39) were surgeons and the remainder were gastroenterologists. Respondents were mostly male (89.5%, n=60) and the majority were either in the 34-42 year or 43-51 year age categories. Most had greater than 8 years' experience at Consultant level.

The majority of respondents worked in a university hospital (58.2%, n=39) and 43.3% (n=29) reported that their institution had between 201-400 patient beds. The majority of those surveyed (82.5%, n=47) reported seeing chronic pancreatitis patients in their practice, and 25% (n=17) reported seeing more than 10 patients per year. Thirty-five percent (n=24) of those surveyed estimated that 5% of their case-load was dedicated to pancreatic diseases. Surgeons and gastroenterologists were asked if their patients had access to a dedicated MDT for chronic pancreatitis patients, of those who answered, 72.4% (n=42) answered that they did not, and 6.8% (n=10) were unsure. According to those with MDT access, 94.1% (n=16) indicated that the team was led by a Surgeon. Results are detailed in Table 5.4.

5.2.3.3. Diagnosis of chronic pancreatitis

Regarding the diagnosis of chronic pancreatitis, the majority of consultants (93%, n=51 reported using computed tomography (CT), followed by magnetic resonance cholangiopancreatography (MRCP) (73%, n=40) and FE-1 (73%, n=40), (more than one response was allowed). Following this were endoscopic ultrasound (EUS) (58.2%, n=32), magnetic resonance imaging (MRI) (36.4%, n=20), serum glucose (29.1%, n=16) and endoscopic retrograde cholangiography (ERCP) (27.3%, n=15) were chosen. Lesser used modalities reported included serum trypsin (9.1%, n=5) and faecal fat (10.9%, n=6). Table 5.5 summarises these results.

5.2.3.4. Knowledge / awareness of guidelines

When questioned about awareness of national or international consensus guidelines for the management of chronic pancreatitis, almost seven in ten specialists (70.9%, n=39) answered that they were not aware of any management guidelines. Of the respondents, only 16 (n=29%) reported being aware of any practice guidelines. Of 17 guidelines specified (more than one answer was permitted), the most often cited were the British Society of Gastroenterology guidelines and Italian Consensus Guidelines (both 0.04%, n=3). Just two (0.03%) of those who specified being aware of any guidelines cited the British Medical Journal Best Practice Guidelines, The American Gastroenterological Association guidelines, and the NICE guidelines (Table 5.6).

5.2.3.5. Recommendations for improvement

In terms of chronic pancreatitis management and areas for potential improvements, respondents from the specialist survey listed the following as areas of importance; pain control (77.6%, n=38), treatment (61.2%, n=30), nutrition (46.9%, n=21), follow-up

(42.9%, n=21), biochemical diagnosis (30.6%, n=15), smoking cessation (24.5%, n=12), radiological diagnosis (22.5%, n=11) and diabetes management (20.4%, n=10).

5.2.3.6. Management of acute pancreatitis

Ninety-one percent (n=50) of respondents said that they see patients with acute pancreatitis on a regular basis. Of those, 65.5% (n=36) reported having follow-up procedures in place for acute pancreatitis patient management in their institutions.

5.2.3.7. Perceptions about the utility of a disease registry

57 specialists responded to the question on whether or not a chronic pancreatitis disease registry would be useful to estimate chronic pancreatitis prevalence. Of those that responded, 73% (n=41) of gastroenterologists and general surgeons answered 'yes' while 21.43% (n=12) were 'unsure' of its usefulness. When asked if they thought a national chronic pancreatitis disease registry would actually be utilised by health professionals, 56% (n=32) agreed that it would be used, 12.4% (n=7) answered no, while 31.4% were 'unsure'. Perceived barriers affecting the utilisation of such a disease registry included 'ease of data acquisition' (50%, n=26), ease of access (46.2%, n=24), relevance to practice (40.4%, n=21), cost (38.5%, n=20), security (17.3%, n=9), confidentiality (15.4%, n=8) and 15% (n=8) answered 'all of the above'.

Gastro and General Surgeon Survey results	N	%
Total surveys sent	248	
Total completed surveys	68	
Incomplete / declined participate No response	180	
Profession		
Gastroenterologist	29	42.7%
Surgeon	39	57.4%
Gender		
Male	60	89.6%
Female	7	10.5%
Age		
0-33 years	2	2.9%
34-42 years	23	34.3%
43-51 years	25	37.3%
>52 years	17	25.4%
Consultant years		
0-3 years	13	19.1%
4-8 years	19	27.9%
>8 years	36	52.9%
What type of institution		
University Hospital	39	58.2%
District / Regional Hospital	19	28.4%
Private Hospital	9	13.4%
Number of beds		
0-200	6	9.0%
201-400	29	43.3%
401-600	21	31.3%
601-800	9	13.4%
>800	2	3.0%
Access to specialist MDT		
Yes	16	27.6%
No	42	72.4%
MDT team led by		
Surgeon	16	94.1%
Gastroenterologist	1	5.9%
Intensivist	0	0
Tertiary referrals		
Yes	27	46.6%
No	29	50.0%
Unsure	2	3.4%
See CP Patients		
Yes	47	82.4%
No	10	17.5%
Aware of CP guidelines		
Yes	16	29.1%
No	39	70.9%
Would a national CP registry be useful		
Yes	41	73.2%
No	3	5.36%
Unsure	12	21.4%
Would a national CP registry be utilised		
Yes	32	56.1%
No	7	12.3%
Unsure	18	31.6%

Table 5.1: Demographic and practice characteristics - gastroenterologist / general surgeon survey

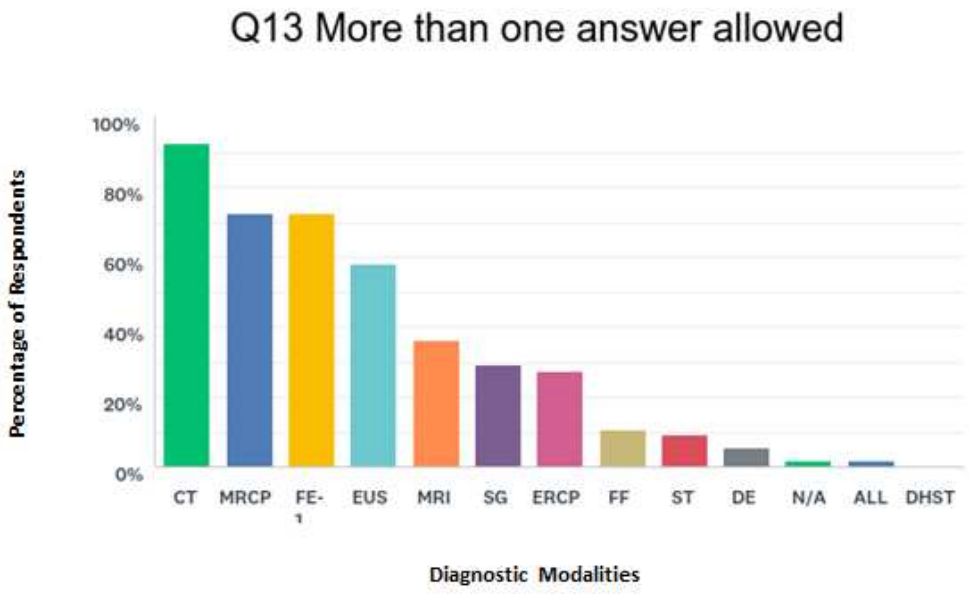

Figure 5.5.2: Methods reported by Surgeons / gastroenterologists when asked how they diagnose chronic pancreatitis

**CT- Computed tomography, MRCP- magnetic resonance cholangiopancreatography, FE-1- faecal elastase-1, EUS- endoscopic ultrasound, MRI- magnetic resonance imaging, SG- serum glucose, ERCP- endoscopic retrograde cholangiopancreatography, FF- faecal fat, ST- serum trypsin, DE- diagnosed elsewhere, N/A- do not see patients, ALL- all of the above, DHST- direct hormonal stimulation testing.*

*(*More than one response was allowed)*

Guideline Name	N	%
Italian consensus guidelines	3	0.04%
BSG guidelines	3	0.04%
BMJ best practice guidelines	2	0.03%
AGA guidelines	2	0.03%
NICE guidelines	2	0.03%
GUT guidelines	1	0.01%
RCSI guidelines	1	0.01%
HPBSA guidelines	1	0.01%
ASGE guidelines	1	0.01%
Swedish guidelines	1	0.01%
Not my speciality	1	0.01%
No answer / missing	55	80.89%

Table 5.2: Guidelines cited by Surgeons / Gastroenterologists

*BSG British Society of Gastroenterology, BMJ British Medical Guidelines, AGA American Gastroenterology Guidelines, NICE National Institute for Health and Care Excellence, RCSI Royal College of Surgeons Ireland, HPBSA Hepatobilary South Africa, ASGE American Society of Gastroentestinal Endoscopy. (*More than once response was allowed).*

5.2.4. Discussion: hospital-based survey

5.2.4.1. Summary of findings

This study highlighted a number of issues regarding hospital-based care for chronic pancreatitis in Ireland. Access to a dedicated multidisciplinary team was notably lacking for more than seven out of ten of respondents. Those in charge of care at hospital level highlighted several key areas of care that require improvement, specifically pain control, treatment, nutrition, along with adequate follow-up. Results showed that the majority of gastroenterologists and surgeons (93%) use computed tomography (CT) to diagnose chronic pancreatitis. A key finding of this study was the poor awareness of practice guidelines. Only 16 of those who responded to the survey were aware of any chronic pancreatitis practice guidelines.

5.2.4.2. Response rate

Unfortunately, the hospital-based survey did not achieve a high response rate and therefore the survey was subject to a level of non-responder bias. This limits the applicability of the findings, which may not be truly representative of the population of hospital-based specialists. There are a various factors which may impact on participation and level of survey response. Reasons for the poor response from hospital-based doctors include; the online survey methodology, lack of time by consultants, or an unwillingness to respond or participate. A level of survey burden may also be true, with growing survey request and time constraints, which limit the ability to participate. It may be that specialists are not interested in endorsing this research area of chronic disease management. Further, factors associated with survey mode, survey design, and survey length may have contributed. Generic emails from academic institutions and societies may have been perceived as unimportant or spam and the survey may have been missed. Beyond some similarities in gender and speciality, an

assessment of potential factors that may have impacted certain specialists to respond versus non-responders was not possible. The response rate, though low, is comparable with two other surveys of specialists ranging from 21% (286) to 30% (287).

In future studies, some changes to methodology are proposed which may potentially increase response rate. Aspects of The Tailored Design Method (TDM) (288) will be incorporated into study design - the efficacy of which is widely recognised to increase response rate. The addition of a paper element into the survey design to create a mixed mode is evidenced as a strategy to minimise non-response. A more personalised approach to the survey is proposed, including the survey being preceded by a mailed contact and correspondence. The current study was constrained in terms of access to the cohort of gastroenterologists and specialists surveyed. The author was unable to contact the respondents directly, therefore limiting the knowledge and control of data collection. In future surveys and to increase response rate, a mixed-mode or paper-based survey utilising the Tailored Design Method (288) is recommended. A third of the sample of specialists and gastroenterologists responded to the current survey, and inferences should be interpreted with due respect to the limitations outlined.

5.2.4.3. Multidisciplinary team (MDT) access

The majority of specialists surveyed identified that their patients had no access to a multidisciplinary team for care. The reasons for this are unclear, and may be attributable to a lack of specialists' services for patients with chronic pancreatitis in certain hospitals in Ireland. The organisation of healthcare with particular focus on how chronic diseases are managed is a key issue. Complex chronic diseases require a variety of health professional competencies, underlying the need for inter - and multidisciplinary effort (3). In a review of the management principles of chronic

pancreatitis (64), optimal patient management requires a multidisciplinary team including, gastroenterologists, surgeons, nurses / clinical nurse specialists, endocrinologists, dietitians, pain management, psychiatrist, social work, and patient support group. According to the Department of Health in Ireland, most patients with chronic diseases encounter fragmented care that does not include all of the elements to reduce the burden of disease for the patient (3). Developing effective models of care for patients with chronic diseases is a key challenge in improving the performance of the health system.

5.2.4.4. Diagnosis of chronic pancreatitis

The majority of specialists used CT to diagnose chronic pancreatitis, followed by MRCP and FE-1. One study which surveyed Dutch gastroenterologists, internists and gastrointestinal surgeons (289), found a wide variation in the reported use of diagnostic modalities, treatment, and screening for chronic pancreatitis. The authors pointed to a lack of evidence and consensus in the literature; however, while this may have been true in the past, there has been a considerable increase in the development and publication in chronic pancreatitis-specific guidelines in the last few years. In the years prior to undertaking this current study, a number of National guidelines have been published on the management of chronic pancreatitis from European countries (117-119, 121, 279), as well as publication of American guidelines on the diagnosis of chronic pancreatitis (122). However, there remains a lack of agreed systematic guidelines to direct a multidisciplinary approach to care in order to achieve excellence in patient care (15). The diagnosis of chronic pancreatitis must be reached by a combination of clinical data, imaging techniques and/or functional tests and these should be used in a complementary method due to often unclear signs and symptoms of clinical presentation. None of the available diagnostic modalities provide an unequivocal diagnosis of chronic pancreatitis, particularly in early stage disease. There

remains some level of discordance in the literature on the best method to diagnose chronic pancreatitis which may contribute to a level of confusion as to best practice. German guidelines (123) stated that an ultrasound scan of the pancreas is the first preference in diagnosis. This is disputed in the Spanish guidelines (120) where authors suggest that ultrasound is only useful for the diagnosis of advanced stages of chronic pancreatitis. The Spanish guidelines (120) advocated the use of CT as the best non-endoscopic imaging technique which can diagnose and localise pancreatic calcifications. The German guidelines (123) stated that CT should be used as a supplementary diagnostic technique for unclear pancreatic changes detected on ultrasound and during endoscopic ultrasound. Furthermore the Spanish guidelines advise that ERCP is useful for detecting pancreatic duct dilation, parenchymal atrophy and focal lesions. Again, this is disputed in the German guidelines where the authors recommend that diagnostic ERCP should not be used due to associated higher morbidity and mortality rates. Interestingly a number of specialists in the current study identified the use of ERCP for the diagnosis of chronic pancreatitis. Again, this indicates the lack of penetrance of updated practice guidelines, reasons for which are unclear.

5.2.4.5. Management of chronic pancreatitis at hospital level

The management of chronic pancreatitis at hospital level begins with the appropriate diagnosis of chronic pancreatitis and determination of disease aetiology. As mentioned earlier a number of chronic pancreatitis consensus guidelines have been published in recent times from Spain, Germany, Belgium, Italy and the US, and these provide clinicians with valuable insights into the numerous complexities of diagnosing and managing chronic pancreatitis patients. The majority of guidelines have focused on the diagnosis of chronic pancreatitis and imaging, radiology and endoscopic options available for diagnosis. In recent years clinical diagnostic tools have seen considerable

improvements and advancements in radiologic and endoscopic modalities to diagnose chronic pancreatitis. There are a number of obvious resource implications to using multiple modalities, some of which may be deemed unnecessary for the diagnosis of chronic pancreatitis. Agreement and consensus must be reached on the best methods to diagnose chronic pancreatitis and which methods may be in current times viewed to be redundant. There also is a need for momentum in raising awareness around the publication of guidelines, and a drive towards increasing uptake of consensus recommendations, to provide best and most appropriate evidence-based patient care.

5.2.4.6. Guideline awareness

The lack of awareness of clinical guidelines for the management of chronic pancreatitis amongst specialists charged with hospital-based management of chronic pancreatitis is worrying. This is despite the fact that a number of international consensus guidelines have been published in the last decade, which are designed to serve as sources of evidence-based professional training and continued education for clinicians. Chronic pancreatitis is a complicated chronic disease and treatment of patients should be centred on treating associated disease complications, careful consideration of potential aetiology, endocrine evaluation and nutrition and lifestyle modifications. To our knowledge, no other studies have specifically examined the awareness of chronic pancreatitis guidelines amongst specialists. To date, only one other study has investigated practice in chronic pancreatitis.

In hindsight, the current study could have benefited from the inclusion of a question on 'guideline use' as awareness of guidelines does not equate to or imply use. It may also be interesting to investigate implementation strategies that may impact on guideline use. There are thought to be a range of factors which impact adherence to guideline in clinical practice, related to characteristics of guideline (290, 291) methods of dissemination, implementation or diffusion (292-294). Other factors are concerned with

the personal characteristics of doctors, for example age, experience, membership of professional association, self-confidence, motivation or attitudes which are thought to impact implementation (295-297).

Adherence to guidelines has been studied for other conditions, such as IBD. A review of clinician's adherence to international guidelines in IBD clinics found an overall adherence to disease management guidelines in 71% of encounters, while discrepancies between guidelines and management occurred in 31% and 42% of patient encounters (298). The authors suggested that gaps between guideline adherence and clinical practice may be reduced by implementing evidence-based clinical pathways.

In a German survey of gastroenterologists regarding the management of Crohn's disease, an overall high adherence to guidelines was found, with the exception of emphasis placed on smoking cessation as a therapeutic strategy (299). A survey of Spanish gastroenterologists evaluated the degree of adherence to European Crohn's and Colitis (ECCO) guidelines and found that there was high overall adherence among both specialised and general gastroenterologists, although specialists performed better regarding diagnosis and follow-up (300). The reasons for the lack of penetrance of chronic pancreatitis guidelines among Irish physicians require further investigation, and certainly, there is an urgent need for education in this area. The development of management guidelines is a costly process in terms of time and resources and requires significant investment in research, assimilation, preparation and review of data. However, this process is essentially redundant unless management guidelines are used correctly by those for whom they are intended. It is clear that the existing guidelines for chronic pancreatitis are not reaching the intended targets in Ireland.

5.2.5. Suggested areas of improvement

5.2.5.1. Treatment and follow-up

A number of specialists identified improvements which were required in the treatment and follow-up of chronic pancreatitis patients, and these are important general aspects of how chronic diseases are effectively managed. The routine care of patients with chronic illnesses often fails to follow evidence-based guidelines or achieve optimal outcomes (301, 302). Despite evidence that the elements of chronic disease management can improve outcomes, they are often inadequately organised or delivered (301). Beyond diagnosis, there are aspects of treatment required to improve outcomes for patients. Comprehensive medical and surgical treatment, follow-up, preventative activities such as smoking cessation, dietary advice, and support of patient's self-care, are intrinsic aspects of chronic disease management (3). Evidence based guidelines and protocols identify elements for care including; well-defined care plans, patient education, scheduled follow-up, preventative follow-up, outcome and adherence monitoring, targeted use of consultations, and step-up approach to protocols (118, 175, 303). Research suggests that when care based on protocol is implemented, outcomes for patients with chronic diseases can be improved, when self-management training and support are combined with appropriately timed follow-up and support (303, 304).

There is a need to focus treatment based on guidelines which has been shown to improve patient outcomes. The present study highlights the lack of knowledge or use of guidelines for the management of chronic pancreatitis in hospital-based care, which is identified as a barrier to effective chronic care management. The study also evidenced the majority of care is not coordinated by a multidisciplinary team, which is of concern in consideration of the collaborative care requirements of chronic pancreatitis patients. Improving chronic care for patients depends on reforming systems for chronic disease management, and implementing guidelines, or adhering to available guideline.

Elements of an effective care system must be advocated to improve care for chronic disease sufferers.

5.2.5.2. Nutrition and dietetic support

The nutritional treatment by pancreatic dietitians is a cornerstone of the management of chronic pancreatitis which has been outlined in many publications and international guidelines (119, 181, 282). Despite this, a number of specialists in the current study highlighted that there was no access to dietetic services in their institution, and that a barrier to patient care was lack of availability and input in patient management from dietitians. This must be viewed as an important, yet actionable barrier to the management of chronic pancreatitis patients and should be addressed in order to improve patient care. As previously discussed it is vital for chronic pancreatitis patients to be managed appropriately by a specialist pancreatic dietitian. There are various important nutrition-related consequences of chronic pancreatitis; pancreatic exocrine insufficiency, malabsorption, maldigestion, steatorrhea, micro- and macronutrient deficiency, osteoporosis, osteopenia, and cachexia. The nutritional management of patients is complex and often exacerbated by ongoing alcohol-intake, smoking, poor diet and social circumstances which impact patient outcomes. Early detection, assessment and intervention in the nutritional care of patients may serve to lessen the risk of further damage and consequences. Services must be put in place for the referral of patients to specialist centres to ensure appropriate and thorough management with a specialist pancreatic multi-disciplinary team.

5.2.5.3. Perceptions of a disease registry

A number of gastroenterologists and general surgeons outlined specific barriers to the utilisation of a disease registry for the surveillance of chronic pancreatitis in Ireland. Barriers included resources, time and cost. Notwithstanding this assertion, the

specialists surveyed recognised the value of disease registries to aid in patient and disease monitoring. In a survey conducted on the use of patient registries in Ireland, Dr Donohue and colleagues (305) reported that many registries operated with very limited resources, and that a failure to implement data standards was found in some registries. The findings of this report recommend the development of registry guidelines and frameworks in Ireland to allow greater coordination of registries, and to improve standards thereby enhancing their role in health service and providing greater security for patient confidentiality. The report also found that, for those involved in registry operation in Ireland, the lack of security of funding was a critical element. In fact, several registries (12%) reported an absolute absence of funding. There were also ethical issues around the lack of a sustainable funding mechanism.

The use of disease registers for research and for planning care and service provision is central to all models of good chronic disease management. The care of patients with chronic disease management would certainly benefit from the use of disease registers in individual practices, services and nationally. While the aim of the current study was not to enquire regarding the use of electronic medical records (EMRs), it is known that within the Irish health system, while GPs do use EMRs, most hospital-based services do not, which is a further significant barrier to achieving good chronic care for these patients. Whilst the current healthcare system in Ireland does not contain unique patient identifiers, the HSE and the Department of Health have planned to roll out eHealth in Ireland introducing a unique health identifier by 2018. This will be aided by the roll out of EMRs across all primary care and hospital settings in the near future, and this has the potential to support safer and more efficient integrated healthcare for patients in Ireland.

5.2.5.4. Future directions hospital-based chronic disease management

A number of important changes must take place in secondary care in order to improve services for patients. As established in the current study, patients with chronic pancreatitis are diagnosed and managed in secondary care, and therefore they must be funded, resourced, staffed, and appropriately supported to be able to manage patients. Patients with chronic diseases such as chronic pancreatitis must have access to the appropriate services to receive the best most appropriate care. For optimal management patients should have access to a multidisciplinary team. A fundamental aspect of patient care is the management of nutritional status, and patients must be able to access the necessary services to treat their disease needs. For acute care further planning and realignment of services between acute hospitals is required.

The publication of management studies and epidemiological data will help to provide an understanding of the extent of the problem in chronic pancreatitis care in Ireland which will in turn increase awareness and support efforts in resourcing this area. Disease surveillance electronically in hospitals may provide valuable information for the development of services for patients.

5.3. Part B– Nationwide survey of general practice management of chronic pancreatitis

5.3.1. Introduction

The variable results from the survey of specialists described in Part A, led to the decision to evaluate practice in general practice. This second survey ascended from the hospital-based survey, and tailored to profession and was aimed at GPs managing chronic pancreatitis in primary care. The purpose of this second survey was to evaluate

knowledge, insight and current practices in the management of chronic pancreatitis at community level.

5.3.2. Materials and method

5.3.2.1. Survey

The study design was a cross-sectional descriptive survey of the management of chronic pancreatitis in general practice in Ireland. The GP survey was designed to specifically target GPs, and included 23 questions. This survey was designed to explore practice primary care in terms of chronic pancreatitis management, practice demographics, patient numbers, GP practice size, number of GPs practicing, access to specialist services, education, guidelines, insights and concerns regarding chronic pancreatitis management, acute pancreatitis patient numbers, and opinions on the development of a national chronic pancreatitis disease registry (perceived need, benefits and barriers).

5.3.2.2. Data collection

The primary care survey was piloted to a group of GPs (n=20) for content analysis, relevance and ease of use. Following this, it was mailed to all GPs throughout the Republic of Ireland, in two separate waves (each 1 month apart). A total of 1,126 surveys were posted, with a letter explaining the scope and purpose of the study in detail. The survey pack included a prepaid stamped addressed envelope. GPs were asked to include their practice stamp on the back of the survey, should they wish to be excluded from repeat survey mailings, all of which features are closely based on the tailored survey methodology (288).

The approximate number of GPs working in the Republic of Ireland is 2,817. Postal addresses of respondents were derived from the Irish Medical directory (which contains information on practicing doctors and surgeons in Ireland) and the National Cervical Check website (which includes an online repository of registered GPs working in the Republic of Ireland). We extracted a 20% block randomisation purposive sample of those names contained online, to equitably represent inner city, deprived, affluent, urban towns, and rural areas.

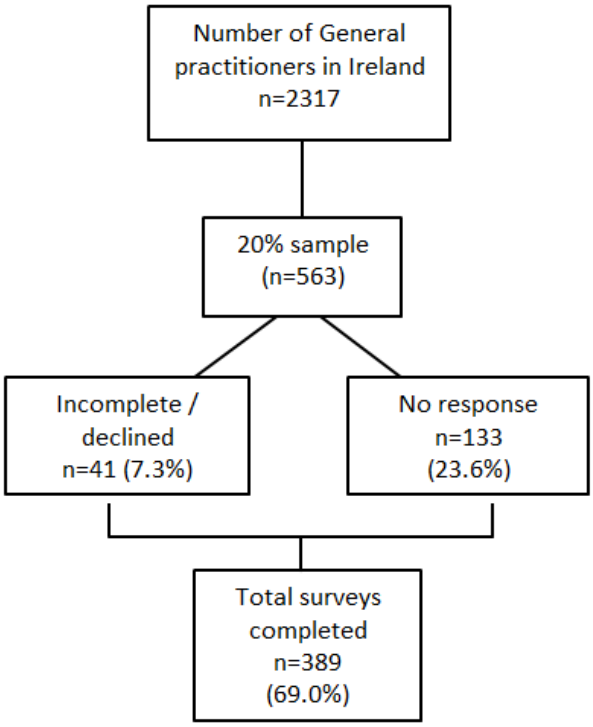

Figure 5.3: General practitioner study flow chart

5.3.3. Results of the GP survey

5.3.3.1. Survey response

In total, 389 GPs completed and returned the survey. This was an overall response rate of 69%. Forty-one blank surveys (7.3%) were returned with GPs' practice stamps

included, which indicated that they wished not to complete the survey and to be removed from the mailing list for future mailings. Two surveys were automatically returned by *An Post* postal delivery service due to vacant addresses.

5.3.3.2. Demographics / practice characteristics

Of the GPs who completed the survey, 48% (n=185) of practices were located in what they classified as 'urban' areas and 30% (n=115) were in 'mixed' areas (both rural and urban). Sixty-two percent (n=236) of GP respondents were male. Most (52%, n=200) were >52 years of age, and 88% (n=341) had greater than 8 years' experience in general practice post qualification. Most (79%, n=305) reported having chronic pancreatitis patients currently in their practice. Over half of respondents (57%, n=219) reported having 1-3 chronic pancreatitis patients currently in their practice. Fifty respondents (12.9%) reported having 4-5 patients with chronic pancreatitis in their care, with a further 7.2% (n=28) having between 5-10 patients in their care. The majority of respondents (43%, n=165) had just one full-time GP in their practice. Seventy-two percent (n=280) of GP practices surveyed did not have a GP trainee or registrar, but 55% (n=213) did train undergraduate medical students. Demographic results are detailed in Table 5.1.

GP Survey	N	%
Total surveys sent	563	
Total completed surveys	389	
Incomplete / declined participate	41	
No response	133	
Practice demographics		
Rural	85	22.1
Urban	185	48.1
Mixed	115	29.9
Gender		
Male	236	61.8
Female	146	38.2
GP age		
0-33 years	10	2.6
34-42 years	85	22.0
43-51 years	91	23.6
>52 years	200	51.8
Years of experience		
0-3 years	14	3.6
4-8 years	32	8.3
>8 years	341	88.1
GP trainee / registrar		
Yes	107	27.6
No	280	72.4
Undergraduate medical students		
Yes	213	55.0
No	174	45.0
Total number of CP patients currently in practice		
0	82	21.2
1-3	219	56.6
4-5	50	12.9
5-10	28	7.2
>10	8	2.1
Access to specialist multidisciplinary team		
Yes	80	20.9
No	165	43.2
Unsure	137	35.9
Aware of CP guidelines		
Yes	15	4.0
No	364	96.0
Would a national CP registry be useful		
Yes	187	49.3
No	23	6.1
Unsure	169	44.6
Would a national CP registry be utilised		
Yes	109	28.8
No	58	15.3
Unsure	212	55.9
Do you have a pancreatitis practice register		
Yes	49	13.4
No	318	86.6

Table 5.3: –General practitioner demographic and practice characteristics

(*GP- general practitioner, CP-chronic pancreatitis)*

5.3.3.3. Management of chronic pancreatitis

On a 5-point Likert scale (ranging from 'very unhappy' (1) to 'very happy' (5)) GPs were asked if they were happy to continue to provide ongoing care to patients with chronic pancreatitis. Over a third of respondents (38%) positioned themselves in the middle of the Likert scale (Figure 1). When asked if a continuing medical education (CME) module on the primary care management of pancreatitis would be useful, the majority (29%) answered "very useful" with a minority (6.2%) selecting "of limited use" (Figure 5.1).

Two in five (43%, n=165) of GPs reported that their patients do not have access to a specially-dedicated MDT for the management of chronic pancreatitis, while 36% (n=137) answered that they were 'unsure' if there was a MDT available to them. Of those that stated that their patients had access to an MDT, most (94%, n=364) stated that it was led by a Gastroenterologist. Almost all GPs (96%, n=364) were unaware of any national or international consensus guidelines for the management of chronic pancreatitis.

When asked about the perceived usefulness of establishing a national disease registry for chronic pancreatitis in Ireland respondents were almost equally divided, 49.3% (n=187) reported that it would be beneficial, with 44% (n=169) stating they were 'unsure' of its benefit. When asked if they thought that clinicians would actually use such a registry, 56% (n=212) reported they were 'unsure' while less than a third (29%, n=109) answered 'yes'. Most (87%, n=318) of those surveyed did not have a practice disease register for patients with pancreatitis. Two in five (41%, n=159) reported that they "never" code for chronic pancreatitis patients in their electronic medical record.

Table 5.4 summarises the responses given to the open-ended question '*is there any particular area of chronic pancreatitis management that you think could be improved on in the Primary Care setting'*. Only one hundred and two (26%) GPs responded to this

question. More than one response was allowed, which were categorised according to theme. The most common perceived improvements required were ‘improved access to the public healthcare system’, ‘access to a chronic pancreatitis MDT’, ‘access specifically to the dietitian’, ‘guidelines for chronic pancreatitis’, and ‘more education’. However, it must be acknowledged that the majority of GPs (73.4%, n=287) did not answer this question and therefore did not identify areas for potential improvement.

One hundred and fifty nine (41%) of GPs responded to the question on perceived barriers to good care for chronic pancreatitis (Table 5.4), with access to public sector services / access to specialist care / access to MDT team and lack of knowledge / GP experience / education / information / guidelines being the most commonly reported answers. However, the majority of GPs (59%, n=230) did not answer this question and therefore did not identify barriers to care. Similarly, Table

5.3.3.4. Management of acute pancreatitis

Regarding acute pancreatitis management, the majority (87%) reported seeing patients with acute pancreatitis in their practice, with 64% stating that they had seen between 1-3 patients with acute pancreatitis in the last 5 years. Two in three (66%) stated there was no follow-up procedures in place for acute pancreatitis patients in their practice.

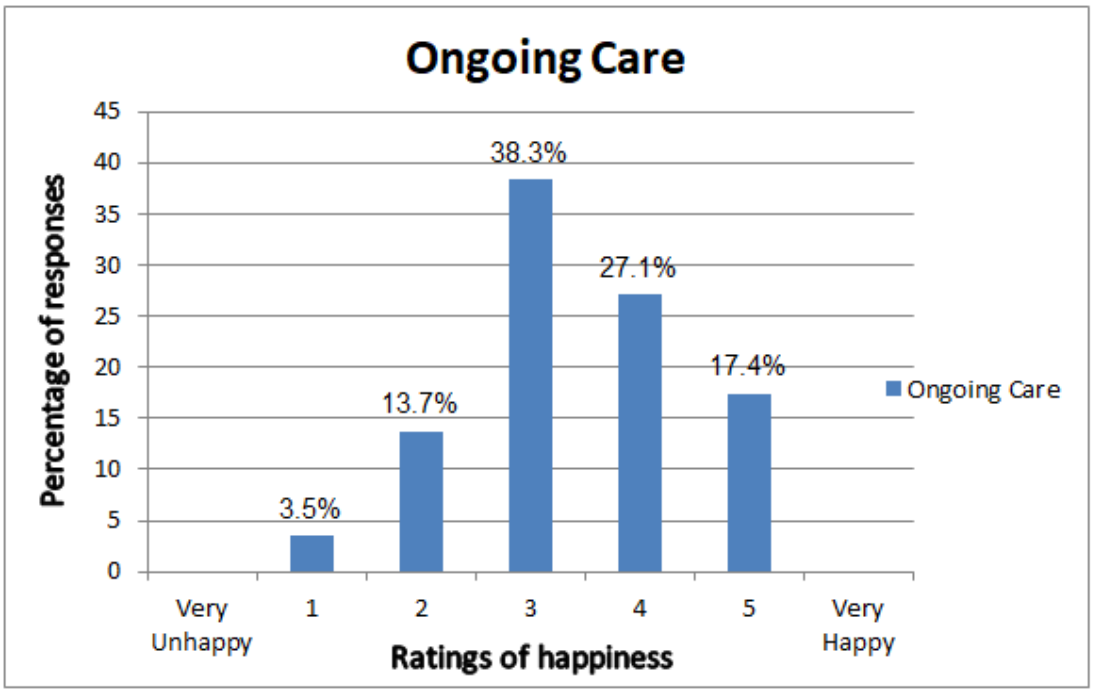

Figure 5.4: General practitioner responses from a 5-point Likert scale showing responses to the question "Are you happy to provide ongoing care to patients with chronic pancreatitis?"

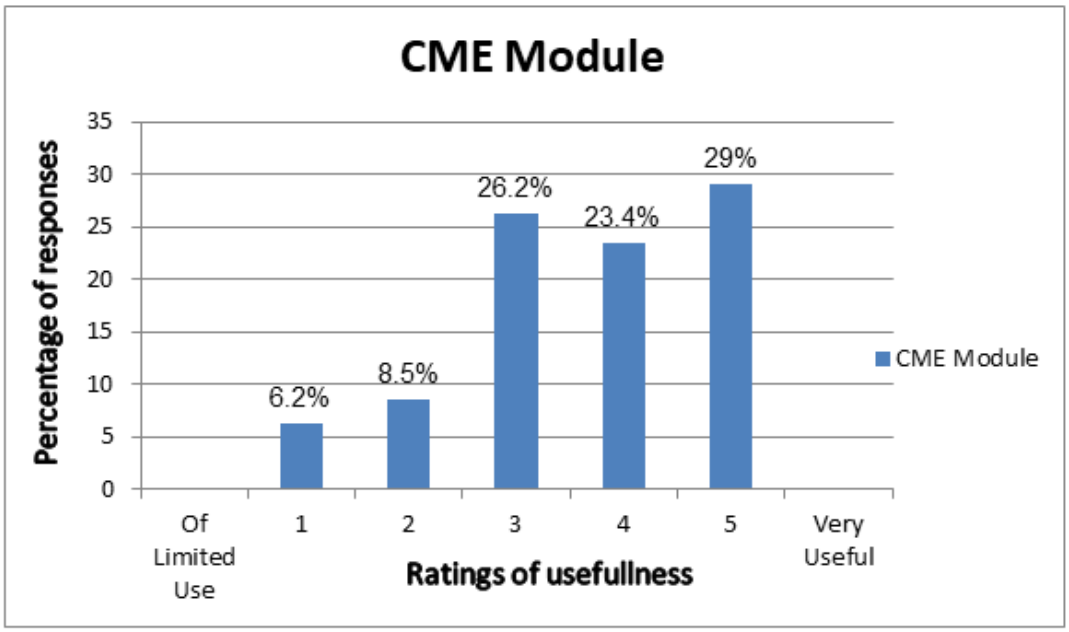

Figure 5.5: General practitioner responses from a 5-point Likert scale showing responses to the question; "How would you rate an online CME module on the primary care management of chronic pancreatitis?"

Suggested improvements	N	%
Number of respondents	102	22.2 (total)
Improved access to public sector health care	25	24.5
Access to a chronic pancreatitis multi-disciplinary care team	23	22.5
Access specifically to dietitian	19	18.6
Guidelines for chronic pancreatitis	19	18.6
More education	19	18.6
Pain management	11	10.8
Alcohol treatment / avoidance / addiction services	10	9.8
Treatment	9	8.8
Increase funding for chronic disease	8	7.8
Combined care plan	7	6.9
Improvements regarding diagnosis	6	5.9
Improved follow-up	4	3.9
Communication	3	2.9
All aspects of care	3	2.9
No answer	287	73.4 (total)

Table 5.4: General practitioners' responses to the question; "Is there any particular area of chronic pancreatitis management that you think could be improved on in the primary care setting?"

Responses are categorised according to theme. 102 GPs responded to this question, and there more than one response was allowed.

Barriers	N	%
Number of respondents	159	40.9 (total)
Access to public sector services / access to specialist care / access to MDT team	54	34.0
Lack of knowledge / GP experience / education / information / guidelines	34	21.4
GP time / too busy	15	9.4
Poor or lack of alcohol support services	13	8.2
Poor or lack of communication between primary & tertiary care	11	5.4
Cost (of chronic care)	10	6.3
Lack of community support services	9	5.7
Poor patient compliance with treatment	7	4.4
No dietitian available	6	3.8
Resources	6	3.8
Difficulties around diagnosis	5	3.2
Chronic disease not adequately funded	5	3.2
Priority given to more common disorders	5	3.2
Difficulties around pain management	4	2.5
No barriers	4	2.5
Demographics / deprived area	3	1.2
Follow-up	3	1.2
Analgesia dependence	3	1.2
No answer	230	59.1 (total)

Table 5.5: General practitioners' responses when asked about 'perceived barriers to good chronic pancreatitis management in primary care'

GP- general practitioner, MDT- multidisciplinary team. Responses are categorised according to theme. 159 GPs responded to the question and more than one answer was allowed.

5.3.3.5. Perceptions about the usefulness of a disease registry

When asked about the perceived benefit of the introduction of a disease registry for the monitoring of chronic pancreatitis in Ireland, half of GPs reported that it would be beneficial, whilst 44% stated they were 'unsure' of its benefit. When asked if GPs would use such a resource, collectively 69.4% (n=270) answered no or unsure, with only less than 30% (n=109) stating that such a registry would be utilised.

5.3.4. Discussion: GP survey

5.3.4.1. Summary of findings

This study is the first to evaluate the management of chronic pancreatitis among those directly responsible for care at community level. Given a robust approach to sampling and a good response rate, results from this survey are representative, and conclusions drawn from them more likely to be generalizable. This study highlights the deficits in primary care in Ireland, and specifically emphasises that chronic pancreatitis is not being managed as a chronic disease in primary care. The majority of GPs were located in urban settings, were male, and had greater than 8 years' experience working as a GP. The majority of GPs had one GP in their practice and did not have registrars or trainees. Many GPs were happy to continue with chronic pancreatitis management in primary care; however barriers were outlined along with suggested improvements which are necessary to assist the management of patients, including guidelines, education and access to specialist services. The majority of GPs were unaware of any guidelines for the management of chronic pancreatitis, despite the largest proportion of GPs having chronic pancreatitis patients in their care. GPs were interested in the prospect of a disease registry but were unclear if such a resource would be utilised.

5.3.4.2. Access to MDT and specialist services

A significant proportion of GPs identified that their patients did not have access to a specialist multidisciplinary team for the management of their disease. Furthermore, GPs outlined important barrier to patient care in the primary care setting was lack of access to specialist services for patients. Due to the complex nature of chronic pancreatitis, patients are seen by specialists and care is planned. However, care may be fragmented between the hospital-based care and in primary care. A recent survey of chronic disease management in primary care demonstrated that the majority of GPs believe that their patients have difficulty getting specialised diagnostic tests, experience long waiting times to see hospital specialists and to receive treatment after diagnosis (176). Additionally, dual surveys of the management of chronic diseases by hospital consultants and GPs reported that there is very inadequate coordination of care between hospital services and GP (176, 306).

5.3.4.3. Management of chronic pancreatitis in primary care

This studied highlighted deficits in the management of chronic pancreatitis in primary care in Ireland. Specifically, the study demonstrated that chronic pancreatitis is not currently being managed, or remunerated, as a chronic disease in primary care. This in contrast to other chronic diseases such as hypertension and diabetes, with the latter only being included in the Irish General Medical Scheme (GMS) contract in 2015, 2 years prior to conducting this study. Acute care, due to its perceived urgency, takes priority over chronic care or preventative care (when services are overstretched in terms of numbers and physician time). A recent study showed that most Irish GPs identified the need for significant changes in the current healthcare system to improve chronic disease management (176). The present GMS contract makes provision for the diagnosis and acute management of illness, but makes no provision (excepting the 2015 amendment for Diabetes Care) for chronic disease management in the context of

current models of care for long term conditions (such as the Chronic Care Model (283, 307) or The Patient Centred Medical Home (308, 309)).

5.3.4.4. Guideline awareness

Poor awareness of guidelines among GPs is concerning in consideration of the fact that the majority of GPs stated that they regularly manage chronic pancreatitis patients in their practice. This is consistent with what is currently known about chronic pancreatitis that the care and management of this condition is often *ad hoc*, and differs considerably across different geographical locations and healthcare settings. The guidelines published on the management on chronic pancreatitis do not include sections on management at primary care level (117-122) nor are there stand-alone primary care chronic pancreatitis guidelines for any other country (of which the author is aware). Nevertheless, a lack of education and guidelines were highlighted by GPs in this survey with 96% (n=364) having no awareness of any guideline for chronic pancreatitis management. When asked about barriers to chronic pancreatitis management in primary care 21% (n= 34) of GPs responded specifying that a lack of knowledge / education / experience / guidelines were obstacles to good care. When asked about suggested improvements to chronic pancreatitis managements 38% (n=19) specified education or guidelines. However, it must be acknowledged that the majority of GPs did not respond to the two questions about barriers or suggested improvements to chronic pancreatitis management in primary care, and therefore the aforementioned findings may not be representative of the entire cohort.

5.3.4.5. Barriers to patient management

The GPs surveyed outlined a number of important barriers to patient management which must be overcome in order to improve services for patients. The majority of GPs identified issues around public sector access, access to specialist care and access to MDT teams. Lack of effective communication between primary and hospital-based care was regularly cited barrier to the effective management of chronic pancreatitis. This was identified by GPs as important factor impacting GPs ability to provide care. Patients may be discharged from hospital to the community without adequate communication on the follow-up needed in primary care, and without knowledge of services available or provided in the community. There appear to be are substantial failures in communication between primary and hospital-based care. Lack of diagnostics at community level is a significant issue that should be addressed as a priority to allow GPs to directly refer patients. GPs inability to directly refer patients for diagnostic tests based on their medical insights was highlighted recently in a national GP conference as a significant obstacle (310). Currently patients attend A&E simply to access vital scans and then attend outpatient appointment because GPs cannot access the necessary diagnostics while hospital-based doctors can (310). There is inadequate coordination of care between hospitals and primary care, with GPs lacking direction on the follow-up care required for these patients, and apparently little access to the MDT for guidance or advice.

Many GPs also noted that whilst chronic pancreatitis is a chronic disease, it is not funded under the GMS contract. Unlike in hospital-based care, chronic disease management is funded however this is not the case in primary care and therefore many GPs provide chronic care to patients at a loss. The Primary Care Strategy (160) was published by the Irish Government in 2001 and advocated the introduction of a range of services and benefits to reform primary care in Ireland. The cornerstone of this policy was to provide better services to patients in the community and to reduce the reliance

on an already overstrained secondary (hospital-based) care. Despite this, there has been little change and significant deficiency still exists in terms of infrastructure, services, staff, resources, communication and integrated care. There are long waiting lists for diagnostic and auxiliary services in Ireland which are obstacles to thorough patient care. GPs are ideally placed in the community to provide preventative, predictive and proactive patient care, however this must be supported by hospitals, and by access to diagnostic and specialist services.

The time requirements of a complex disease such as chronic pancreatitis for those providing a primary care service should not be underestimated. 'Lack of time' was a frequently cited by GPs as an obstacle to good management of chronic pancreatitis in primary care. In a US study, the 'top-ten' chronic diseases were estimated to cost 828 hours per year, equivalent to 3.5 hours a day. This was under the premise that the disease was stable and in good control (311). Notably, the 'top-ten' disease list discussed in the study included both diabetes, and osteoporosis, both of which are common complications of chronic pancreatitis.

5.3.4.6. Nutrition management in primary care

The lack of access to dietetic support is a concern as nutrition in chronic pancreatitis has previously been described as a problem area (312). PEI leads to malabsorption of fat, protein and carbohydrate resulting in steatorrhoea and creatorrhoea which results in abdominal discomfort, weight loss and nutritional deficiencies (111, 313). Early detection and effective treatment of PEI using pancreatic enzyme replacement therapy is fundamental to the management of this condition, and to prevent worsening symptoms. The development of PEI may cause secondary complications such as vitamin deficiency and osteoporosis and may lead to the development of other conditions such as cachexia; - attention must be focussed on recognising

complications early to institute treatment to reduce the risk of further damage. This requires careful prescription of PERT, frequent monitoring, and evaluation of outcomes. A study from the Netherlands (127) showed that PERT is underused and under-prescribed for patients with chronic pancreatitis, and given the results of the current study, there is no reason to suggest that there is better management in Ireland. Along with adequate PERT, analgesic agents, alcohol / tobacco abstinence, and appropriate dietetic counselling are among the first-line medical options for patients with chronic pancreatitis (117). Nutritional management should be coordinated and structured, encompassing endocrine, exocrine evaluation as well as dietary assessment, anthropometrics, biochemical evaluation, and assessment of bone health (113). The availability of a specialist pancreatic dietitian in primary, as well as hospital-based care is therefore a crucial part of the management of patients with chronic pancreatitis.

5.3.5. Recommendations for improvement

The GPs surveyed highlighted a number of potential areas for improvement which could augment the care of chronic pancreatitis patients in primary care. Again many of the suggested improvements reflect the barriers which GPs face in primary care when managing chronic disease patients. GPs outlined the need for improved access to specialist services, access to a chronic pancreatitis multidisciplinary team, access to a dietician and guidelines and education. The divide between primary and secondary care in Ireland, in terms of chronic disease management is apparent, and there is a lack of integration. Much of the chronic disease management which takes place in the expensive hospital setting can be delivered in the community at a lower cost and greater convenience to the patient (310). However, this requires a substantial increase in capacity and resources in the community to assist GPs. There are significant communication issues between primary and secondary care with patients discharged to the community with little communication or supports in place. There is a need to

define and improve patient care pathways for integrated community healthcare services. There is also need to provide better information and raise awareness for health professionals and patients on services available at community level. Properly resources and supported GP-led primary care is paramount to the transformation of the Irish healthcare system which can improve patient outcomes and wellbeing whilst also reducing cost and pressure on secondary care services.

5.3.6. Disease registry

Regarding the development of a national chronic pancreatitis disease registry, while some agreed that it would be useful to estimate disease prevalence, a sizable proportion of both GPs and gastroenterologists and general surgeons suggested that it would not be utilised by health professionals and that there would be barriers to its effective implementation, including time, necessity, cost, resources, confidentiality, security, maintenance, and ease of data acquisition. Trotter (314) outlined the benefits of a patient registry from a community-based physician perspective, including the contribution to knowledge of a disease and its management, and access best-practice data to aid disease management. The benefits of patient registries for the management of chronic conditions, and the facilitation of multidisciplinary working in the coordination of patient care, are clear. However, results from the current study indicate that a number of important barriers exist that would impede the development of a chronic pancreatitis disease registry. There was an apparent level of disagreement in the utility of such a resource from those surveyed.

In Ireland, the ICGP have published primary care guidelines on various topics, including asthma, chronic obstructive pulmonary disease, diabetes, chronic kidney disease, coeliac disease, - but not chronic pancreatitis. With this in mind, Part C of this chapter describes the development of primary care guidelines for chronic pancreatitis.

5.3.7. Future directions

Notably, a substantial number of Irish GPs reported being unhappy to continue with the current level of care of chronic pancreatitis patients in primary care. In addition, they specified a need for improved access to public sector care and specialist multidisciplinary team management, as well as specialist dietetic intervention, pain management and alcohol/addiction services. These responses were mirrored when asked about the barriers to providing good chronic pancreatitis management in primary care, with poor public sector and multidisciplinary access being frequently cited, along with a lack (or poor awareness) of guidelines, lack of education, experience, knowledge and information. Both GPs and specialists identified that there is a lack of supports for patients including alcohol abstinence programmes, particularly at community level.

Access to alcohol cessation support is a fundamental part of care for both primary and hospital-based management which must be developed in Ireland in order to meet the needs of patients. Alcohol abstinence in chronic pancreatitis may reduce pain, slows disease progression, reduces the likelihood of complications, and prolongs life (64, 315).

Chronic disease management must be included in the new GP contract to properly fund and resource chronic disease care in Ireland. The care of patients with chronic diseases is complicated by multimorbidity, and the high burden of acute care of chronic conditions. The Irish primary care sector is undergoing a major crisis due to lack of funding, insufficient resources and issues of GP retention. The Sláintecare report (316) which was published by the Houses of The Oireachtas in May 2017 reported the Irish Government's vision in the expansion of the primary care sector in Ireland. Despite this, the publication in December 2017 of the National Service Plan by the HSE (162) makes no provision for the capacity issues in Irish general practice, and have allocated only €25million to redevelop a chronically underfunded and under-resourced sector. The extent of underfunding in Irish general practice is a gravely serious issue which

needs to be addressed immediately. In order to properly care for patients with chronic conditions, the provision of chronic care must be properly funded and resourced.

5.3.8. Strengths and limitations of the two surveys of practice

5.3.8.1. Study limitations

As with all surveys, there were several important limitations that must be outlined. The author made an assumption that the respondents would be representative of all gastroenterologists/surgeons and GPs working in Ireland. However, those who chose not to reply may have more or less knowledge than the respondents, and this introduces an obvious bias. The low response rate from the gastroenterologist / general surgeon survey is also identified and the data obtained is limited in applicability. The use of only survey mode may have limited response rate. The lack of a personalised approach may also have resulted in a lower response rate. In addition, as this is the first study of this nature, we designed the survey specifically for this project, and therefore it is not a validated tool which is a limiting factor.

5.3.8.2. Study strengths

This is the first study of this kind in Ireland, and to the author's knowledge among the first in the UK, and it provides valuable information related to the management of chronic pancreatitis. The survey is the first of its kind for this patient group, and represents an important step in improving understanding about the management of chronic pancreatitis in both primary and hospital-based care. Both surveys were piloted for purpose and use and amended where necessary. The GP survey achieved a particularly high response rate of 69%, reaching a sizeable number of Irish GPs across various settings. The tailored design method which was adopted for use following the

poor response rate, resulted in a high response rate from the GP cohort, and it is suggested for use in future surveys. The results of the study have the potential to be extrapolated to other similar regions and countries, such as the UK. Despite the hospital based survey achieving a low response rate, limitations have been identified, and methods to improve future efforts have been outlined.

5.3.9. Conclusion of surveys

As an inflammatory disease of the pancreas with indefinite pathogenesis, multiple aetiologies and varied clinical manifestations, chronic pancreatitis results in many potential complications for those affected. Due to diverse symptomology and uncertain clinical course, diagnosis is often delayed. This two-part study described the deficits and barriers identified by primary care physicians and gastroenterologists /surgeons regarding the management of chronic pancreatitis in Ireland. Specifically, there is poor awareness of guidelines and a lack of coordinated management in secondary care, including poor access to specialist services including dietitian, and multidisciplinary teams. There is also uncoordinated management between primary and secondary care, with GPs facing difficulty with specialists and specialist service access, impacting on the management of chronically ill patients. A high number of GPs reported being unhappy to continue with the current levels of care to these patients, and specified a need for increased education, resourcing and payment for chronic disease management. These findings, which are applicable not only to Ireland, but too many other European Countries with comparable healthcare models, highlight important system deficiencies regarding the management of patients with this progressive, chronic disease.

The insights and problems identified in the course of these studies, as well active collaboration with the Quality in Practice Sub Committee at the ICGP, led to the

development of the first primary care guidelines for chronic pancreatitis. The development of these guidelines is described in Part C of this chapter.

5. PART C – The development of guidelines for the management of chronic pancreatitis in primary care

5.5. Introduction

As described in Parts A and B of this chapter, there are multiple guidelines for hospital-based diagnosis and management of chronic pancreatitis, however there is an absolute lack of guidelines at community level. Results from the general practitioner and gastroenterologist / surgeon surveys highlighted a clear lack of knowledge regarding the management of chronic pancreatitis in both primary and tertiary level in Ireland. Findings from the survey of primary care outlined barriers to effective care, and a clear desire by GPs to improve care provided. These findings led the author, in collaboration with the Irish College of General Practitioners (ICGP), to devise a Quick-Reference Guide (QRG) to support GPs with the management of chronic pancreatitis in primary care (124).

5.5.1. Guidelines for other conditions

A number of QRG guidelines exist for conditions such as chronic obstructive pulmonary disease (COPD), asthma, coeliac disease, diabetes, cardiovascular disease and dementia. These guidelines were developed by specialists and tailored to the specific needs of GPs in managing patients in primary care. It is a stipulation of the publication of these guidelines that they be updated by the author every 3 years to keep up-to-date with best-available research instructing care.

5.6. Objectives

The objective of the QRG is to provide GPs with current, evidence based, clear information on the management of chronic pancreatitis in primary care. This also included the reliable provision of referral to specialist centres within Ireland.

5.7. Methods

The ICGP QRGs are guidance documents, created by the ICGP Quality in Practice (QIP) committee in collaboration with authors on clinical and non-clinical topics of relevance to GPs. The need for the guidelines arose from the 2-part survey of professionals, and the author held discussions with the ICGP to propose the creation of chronic pancreatitis-specific guidelines in primary care. The ICGP quick reference guideline template contains evidence and recommendations which are graded according to levels of evidence (Level 1-5) and grades of recommendations (Grades A-C) respectively. This grading system is an adaptation of the revised Oxford Centre 2011 Levels of Evidence (317).

The guidelines were developed in a 9-month process (between March 2017 and November 2017)

The steps in the process were as follows:

1. A guideline proposal, outlining the plan for the project, was sent to the ICGP Quality in Practice (QIP) committee for review.
2. The proposal was accepted and permission was granted by the ICGP for the author to lead in the design of the guidelines
3. Guidelines were drafted according to existing ICGP quick-reference guidelines, including the following parameters: introduction, background, aims of the guideline document, key points / recommendations, references, appendices

4. The author engaged in a formative process involving ICGP committee review, interaction and feedback to provide a concise, evidence-based document, which is primarily GP-focussed.
5. There were routine formal reviews and revision of draft recommendations with a focus on developing guidelines that were concise, easy-to-read, and evidence based guidelines.
6. Following a number of reviews by the committee, and several revisions, the final document was agreed by all stakeholders in the project.
7. The guidelines were uploaded onto the ICGP website (124)
8. To ensure dissemination to the target audience, the newly-developed guidelines were publicised at a national ICGP conference (The 2017 ICGP Winter Conference).

5.8. The management of chronic pancreatitis in primary care QRG

Following the 9-month process, the Management of Chronic Pancreatitis QRG was published as a 13-page guidance document detailing the management of chronic pancreatitis in general practice

5.8.1. Pre-diagnosis

The document contains evidence-based information on aetiology, signs and symptoms, and diagnosis, along with an algorithm for GP management of chronic pancreatitis which outlines methods of step-up referral to specialist services if required (Figure 5.6).

5.8.2. Post diagnosis

Following definitive chronic pancreatitis diagnosis (which can only take place in the hospital setting) the management principles for GPs thereafter are provided in detail including; chronic pain management, exocrine / endocrine evaluation and management, nutritional status, bone health management, smoking and alcohol abstinence, patient education, support and self-management, suggested follow-up, and referral to specialist services.

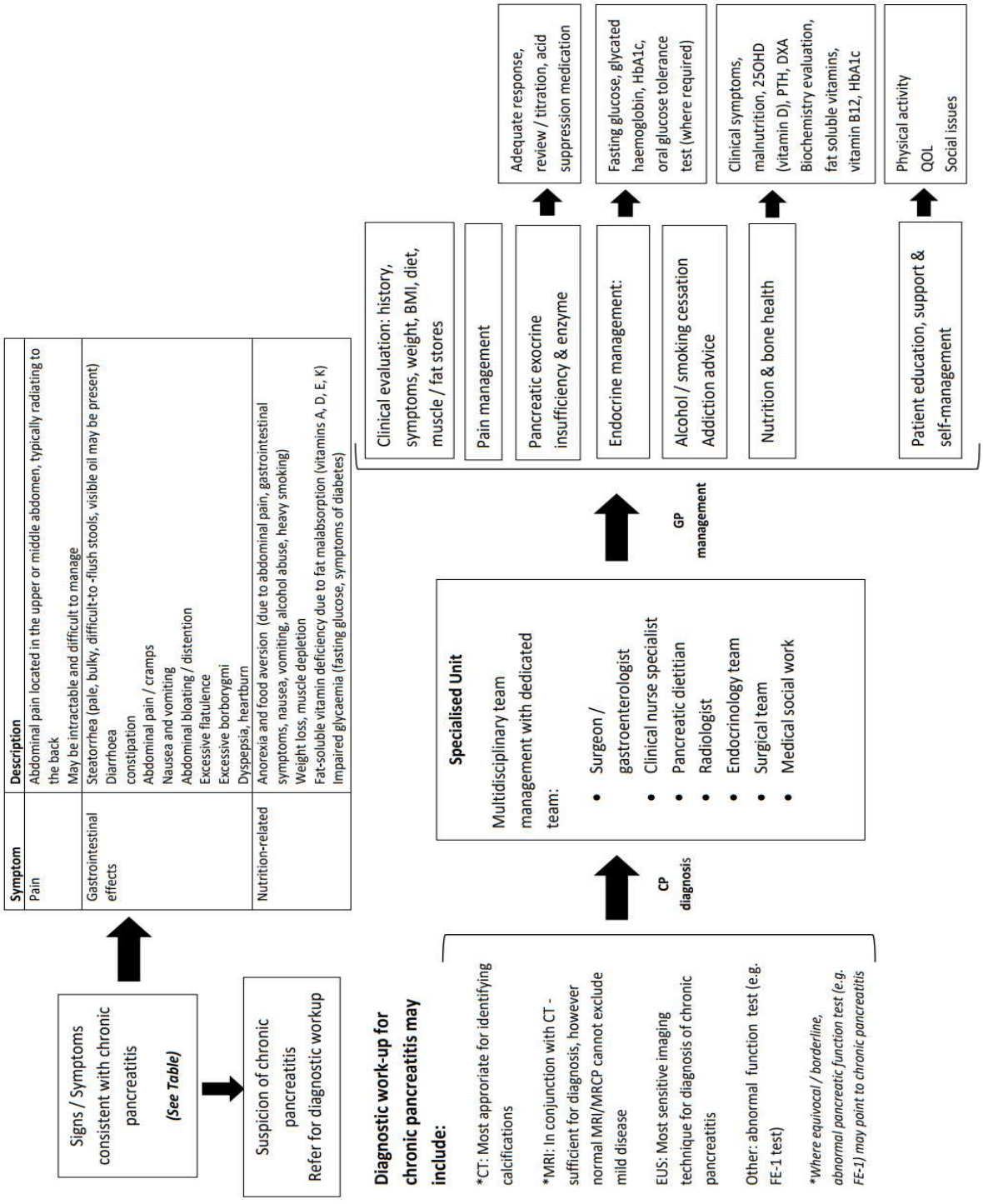

Figure 5.1: ICGP QRG for Chronic Pancreatitis management: Algorithm for the management of chronic pancreatitis in primary care

CT- computed tomography, MRI- magnetic resonance imaging, MRCP- magnetic resonance cholangiopancreatography, EUS- endoscopic ultrasound, FE-1- faecal elastase-1 test, QOL- quality of life.

5.9. Relevance to practice

Chronic pancreatitis has significant life-long health and socioeconomic consequences. GPs, along with hospital-based physicians, play an integral role in overall disease management. Patients require ongoing multimodal follow-up and additional aspects of good chronic care include consultation, providing appropriate high-quality information and confirming good care coordination, particularly during care transitions. These are the first primary care chronic pancreatitis guidelines to be developed for Ireland and, at the time of writing, were being rolled out at a National level. They are freely available for download from the ICGP website (124). The availability of evidence-based information will assist GPs in clarifying any ambiguity in the management of chronic pancreatitis in the community setting, whilst providing them referral information to the specialist clinics and centres nationally.

5.10. General conclusion - Part A, B and C

Part A of this chapter showed for the first time that there are disparities which exist in the management of chronic pancreatitis in Ireland. Specifically, there were significant deficits in the management of chronic pancreatitis in hospital-based care in Ireland. There was a lack of specialist management services available for chronic pancreatitis patients. The majority of specialists stated that there was no multidisciplinary team for the management of patients. Importantly, many of the specialists specified there were no dietitian services available to their patients with chronic pancreatitis. The survey showed that there was a lack of knowledge or awareness of guidelines for the management of chronic pancreatitis in hospital-based care, which is of particular importance. The deficits in guideline knowledge and use in hospital-based care may represent a lack of uptake of the available clinical practice guidelines. Despite the publication of a number of management guidelines for chronic pancreatitis over the last

number of years, the uptake of recommendations into clinical practice is slow or inconsistent.

Part B of this chapter showed similar results including lack of knowledge of guidelines and deficiencies in the management of chronic pancreatitis in primary care. Importantly, the study identified that chronic pancreatitis is not currently being treated or remunerated as a chronic disease in the Irish healthcare system. To conduct a clinical investigation of general practitioners practice and management compared to guidelines would neither be correct or useful as the available guidelines instruct the management in the hospital setting with little or no emphasis on patient management or follow-up in primary care.

The findings of the two surveys combined indicated an important gap in research and clinical management. To address this paucity, Part C of this chapter described the design and implementation of a quick-reference practice guideline for the primary care management of chronic pancreatitis. The availability of clinical practice guidelines for general practitioners provides a template for which practice may be measured against. For patients with chronic pancreatitis this represents an important step in ensuring evidence-based clinical practice and quality patient care.

6. Chapter 6 – An epidemiological study of chronic pancreatitis in Ireland

This chapter describes a study of two parts.

Part A of this chapter describes a study on the epidemiology of chronic pancreatitis in Ireland which, as discussed briefly in chapter 5, has not been thoroughly investigated worldwide. This was an observational study of hospital discharges and patient activity associated with chronic pancreatitis in Ireland over a five-year period. A nationwide retrospective study of all in-patient discharges from acute public hospitals in Ireland was performed. By searching an administrative database of hospital discharges in Ireland, data were extracted for the years 2009-2013 inclusive.

Part B of this chapter describes a systematic review of the epidemiology of chronic pancreatitis internationally, with a specific focus on prevalence and hospitalisation rates.

6.1. General introduction

Epidemiological descriptions of chronic pancreatitis have changed over time, however, the number of studies analysing the population-based frequency of disease are scarce. Disease 'prevalence' refers to the total number of individuals in a population who have a disease or health condition at a specific period of time, represented as a percentage of the population and therefore is a measure of how widespread a disease is. 'Incidence' refers to the number of individuals who develop a specific disease or health related event during a particular period of time. Epidemiological studies are lacking for many countries worldwide, outside of Asia. A small number of published data have come from small regional or single centre reports in Europe, and North America. In Asia, seven consecutive nationwide surveys have been conducted since 1970, and have shown a consistent increase in the prevalence and incidence of chronic pancreatitis. Outside of this series, the frequency of chronic pancreatitis in different populations has not been recurrently documented.

As mentioned in Chapter 2, while there have been advances in a number of areas of chronic pancreatitis in recent times, there are certain areas where knowledge is lacking. The scale of chronic pancreatitis has not been measured previously in Ireland, and therefore the burden of disease is unclear. Population-based frequency of the disease is required to highlight healthcare service and budgetary consideration. The Asian series of epidemiological studies has demonstrated that both the incidence and prevalence of chronic pancreatitis are increasing (39, 137-139). Reasons for these observed increases have been several fold, including increased alcohol consumption (318), an increase in the occurrence of gallstone related pancreatitis, improvements in diagnostic accuracy, interventional treatments, and increased pancreatic enzyme testing (45, 115, 319). In Ireland there has been a rise in the number of hospital admissions for acute pancreatitis (43, 135) which mirrors the data from other countries (40, 320-324). As detailed in earlier chapters, acute pancreatitis is known to lead to

chronic pancreatitis over a number of years. Considering the increase in prevalence and incidence of chronic pancreatitis in other jurisdictions, and documented increase in acute pancreatitis in Ireland and worldwide, there is no reason not to speculate that the same is true for chronic pancreatitis. As detailed in Chapter 3, chronic pancreatitis is known to occur commonly in cystic-fibrosis related gene mutation carriers. Ireland is known to lead in cystic fibrosis gene mutation carrier-prevalence worldwide, with 1:19 of the population affected (250). This is in combination with the already well-known high *per capita* alcohol consumption that exists in Ireland; with alcohol known to be the principal environmental risk factor for the development of chronic pancreatitis. It is not therefore inconceivable that there may be important numbers of patients with chronic pancreatitis in Ireland. There is need to assess the population-based burden of chronic pancreatitis in Ireland, to compare the prevalence with different populations, and to examine trends in disease prevalence and aetiology over time. These factors need to be understood in order to contextualise and disseminate previous and current research on chronic pancreatitis in Ireland. There is also need to understand the basis of this disease in Ireland, in order to effect change in management. National data on chronic pancreatitis are required to guide service planning and policy development, and to plan chronic disease management programmes. Part A which follows describes an epidemiological study of chronic pancreatitis in Ireland undertaken to respond to this research gap. This is followed by Part B, which describes a systematic review of available epidemiological studies to evaluate findings, and contextualise the Irish data amongst those available worldwide.

6.2. PART A- An epidemiological study of chronic pancreatitis in Ireland

6.2.1. Introduction

Epidemiological studies of chronic pancreatitis have evolved over time. Early reports of disease, from 1940's to 1990's described the disease, the clinical picture and natural course, in small select cohorts of patients. These empirical studies have led to understanding of the disease today. In the last quarter century, studies have focused on describing population-based frequency of chronic pancreatitis, disease aetiology in different populations, and the effects of environmental and genetic factors on findings. In order to review the epidemiology of chronic pancreatitis, it is important to highlight some changes that have taken place. In the past 30 years great strides have been made on improving diagnostic accuracy of chronic pancreatitis. In the present day chronic pancreatitis is diagnosed using high-resolution CT, MRI and EUS, and the importance of genetic analysis in diagnosis has also been accepted. It is likely that in earlier studies relying on poor sensitivity equipment including earlier generation CT, diagnosis was confirmed only in the presence of advanced stage morphological changes (325). Therefore, it is plausible that diagnosis now takes place at an earlier stage, by detecting subtle morphological pancreatic changes, however; the impact of improvement in diagnostic techniques on the epidemiology of chronic pancreatitis has not been empirically studied (325).

6.2.2. Prior worldwide studies examining prevalence

Estimating prevalence and incidence rates are a fundamental component in epidemiological studies. A small number of studies worldwide have reported on the prevalence of chronic pancreatitis, which is variable. In Europe chronic pancreatitis rates are estimated at 11.7-49.3 per 100,000 (133, 134). A number of these studies

utilised surveys of specialists, hospital departments or primary care physicians to estimate the prevalence of chronic pancreatitis, and the use of this methodology yielded fluctuating rates from 17.0 to 49.3 per 100,000 of population (326-329). One study in Europe used national patient-linked registry data to evaluate the prevalence of chronic pancreatitis which was estimated to be lower, at 17.0 per 100,000 (133). In Asian countries, the prevalence of chronic pancreatitis has been estimated multiple times from 1970-2014 using a series of nationwide surveys. In Japan, authors in these repeated surveys have demonstrated increasing prevalence rates of chronic pancreatitis ranging from 28.5 to 52.4 per 100,000 (135-138), while in China the prevalence has also risen from 3.08 to 13.52 per 100,000 (139). The prevalence in Southern India was notably highest at 125 per 100,000, which was estimated through a regional field study (140, 141). In this specific study the high prevalence was attributed to an environmental risk factor (high cassava consumption) which was assumed the main aetiological factor and thought to result in a form of injury noted to be 'tropical pancreatitis.

Despite a population of 325 million in 2017, studies from the US are notably few. Only one regional study has been carried out on prevalence of chronic pancreatitis, in one county in the US, where it is reported to be 41.8 per 100,000 (82). Differences in reported prevalence rates worldwide may be largely attributed to methodological differences in data collection methods. Between-country aetiological differences in chronic pancreatitis may also be a factor in the variable prevalence reported. This may also be due to country to country variance in alcohol consumption among different populations. There is a known higher prevalence of idiopathic aetiologies in countries from the Indian subcontinent (141, 330) and alcohol aetiologies have been reported more often in some areas of Europe (326, 331) and America (94, 95).

6.2.3. Prior worldwide studies examining incidence

The reported incidence of chronic pancreatitis in Europe is 2.1 to 13.4 per 100,000 of population (142, 326, 327, 331-335). In the US, the incidence of chronic pancreatitis has increased from 3.3 per 100,000 population in 1940-1969 (144) to 4.0 per 100,000 population in 1977-2006 (82). The incidence in the US appears lower than Europe and the reasons for this are unclear. Since alcohol consumption and smoking are stable or declining in many countries the differences are likely to represent better diagnostics in more recent studies and changes in methodologies. In Asia, between the years 1994 to 2014, the incidence of chronic pancreatitis increased from 5.4 to 14.4 per 100,000 (135-138).

6.2.4. Hospitalisation of chronic pancreatitis worldwide

Sparse data regarding hospitalisation rates for chronic pancreatitis are available worldwide. However, from the available studies it is clear that hospitalisations are increasing in line with increasing prevalence and incidence. In the UK the rate of hospital admissions increased between 1962-1964 (335), and the age-standardised hospital admission rates for chronic pancreatitis doubled between 1989/1990 and 1999/2000 (41). Two American studies have reported that hospitalisations for chronic pancreatitis have changed minimally or remained stable from 1988-2005 (336, 337). Two more recent American studies have reported a decline in hospitalisation, one (338) from 8 to 4.5 per 100,000 population, and another reporting a reduction of 4800 admissions between 2002 and 2010 (339). In the Netherlands, hospital admissions for chronic pancreatitis increased by 75.4% between 1992 and 2004 (340).

In summary, studies worldwide estimating the prevalence, incidence and hospitalisations of chronic pancreatitis have been published. However, much of the

published studies have used ostensibly different methods of estimation (such as surveys of health professionals or chart reviews), while only a small number utilised national databases or administrative databases. In some cases, prevalence and/or incidence was determined using data from a single centre, or within a small geographical region. Single centre case series, especially from tertiary or referral centres run the risk of including potentially sicker and more complicated patients which may not be indicative of the population as a whole and might facilitate population bias. There is also the possibility of a level of prevalence-incidence bias in epidemiological studies, and this occurs when the very sick, the very well (or both) are erroneously excluded from a study. This may result in a disease appearing less severe if patients who have died are excluded, or conversely excluding patients who have recovered, making the condition look more severe (341, 342). Therefore, severe diseases may be overrepresented, and this should be considered (343). Furthermore, a great number of these studies have collected data from many years ago, using different diagnostic criteria, limiting comparison with recent estimates. There are no data for Ireland, and only small, regional estimates for the UK. This constitutes a significant research gap.

6.2.5. Chronic disease in Ireland

According to the World Health Organisation (WHO), by 2020 chronic diseases will rise by 57% and are expected to account for three quarters of all deaths worldwide (148). In Ireland, 1.8 million bed days were used annually (directly or as a contributory factor) by patients with chronic diseases (153). According to governmental healthcare policy in Ireland, quality assurance should be a central concept to chronic disease management programmes (3). This should include the routine and serial measurement of incidence, prevalence and hospital utilisation data and clinical outcomes, monitored systematically at local, regional and national levels (344). In general, chronic disease care in Ireland is

expected to be pressured by the increase in persons aged >65 years (20,000 per year increase) (345). Therefore, the quantification of the epidemiology and hospitalisation of chronic pancreatitis in Ireland is required to guide appropriate and informed chronic disease management. To achieve this, the Hospital Inpatient Enquiry scheme (HIPE) may be used.

6.3. Hospital inpatient enquiry system (HIPE)

6.3.1. Background

Established in 1971, the HIPE is a computerised health information system designed to collect clinical and administrative data on discharges from, and deaths in, acute public hospitals in Ireland. HIPE is the principal source of national data on hospital and discharge activity and morbidity statistics for acute hospitals, and it collects information on hospital day cases and in-patients. Since 1990, the management of this system was contracted by the Department of Health and Children to The Economic and Social Research Institute (ESRI) (namely The Health Research and Information Division), where the HIPE unit was responsible for overseeing the collection, coding, input, quality, processing and reporting of data from participating hospitals. The National Perinatal Reporting System (NPRS) in Ireland provides neonatal statistics on perinatal events, in particular data on pregnancy outcomes, perinatal mortality and important aspects of perinatal care. HIPE and the NPRS provide training on clinical coding to hospital staff, in addition to developing and supporting the relevant software requirements.

The National Casemix Programme was introduced in Ireland in 1993 which was developed after a recommendation from the Commission on Health Funding. The purpose was to fund hospitals based on their activities, and the diagnosis related group (DRG) is used to determine the level of funding. Casemix is the comparison of activity

and cost between hospitals, and the information gathered is shared by all hospitals participating in the programme to allow comparison of performance. This, in turn, facilitates hospitals to examine county of residence data, age profiles for treatment, readmission rates, number of visits per patient-per year, and whether patients are being treated on an inpatient or day case basis (both in their own hospital and other hospitals). Casemix works by coding individual hospital activity and by accessing specialty costs programme which examines hospital costs. Cost data is based on information derived from the audited accounts of the hospitals participating and broken down across cost centres (theatre, nursing, laboratory etc.). These costs are then allocated to the DRGs, which provides an average cost per case. On the 1st of January 2014, the National Casemix Programme and the Health Research and Information Division of the ESRI amalgamated to become the Health Pricing Office (HPO). The HPO now oversees all the functions associated with the operation of the HIPE database.

All 54 acute public hospitals in Ireland partake in HIPE, reporting on over 1.5 million records annually and representing 100% of public hospital coverage. There are 19 private hospitals within the Republic of Ireland providing general medicine, general elective surgery, obstetrics, sports injury clinics, and mental health services. These private hospitals do not currently participate in HIPE reporting. In Ireland, while the exact figure is not known, it is estimated that less than 20% of service activity occurs in private hospitals (Private Hospitals Association, private correspondence). Clinical activity in private hospitals is mainly elective care, and there are no private hospitals in Ireland with a designated pancreatitis service. Therefore, the vast majority of patients with pancreatitis who hold private health insurance are managed within the public health service, and therefore captured by the HIPE system.

6.3.2. The purpose of the HIPE system

HIPE information is used by the Department of Health and the Health Service Executive (HSE) in the planning, provision and measurement of acute hospital activity. HIPE statistics are used extensively by policymakers, clinicians, and researchers for epidemiological studies, hospital activity statistics, population profiles at regional level, quality assurance, market research, and drug trials.

6.3.3. Access to the HIPE system

HIPE statistics are available through a number of channels. National statistics are available in aggregated form, thus ensuring patient confidentiality. For this study, access to 'raw' un-anonymised HIPE data for research purposes was sought through HPO. However, HPO confirmed it was not possible to gain access to this data, due to the risk of a breach of patient confidentiality. 'Raw' data would enable an in-depth and thorough analysis of individual patients with chronic pancreatitis, including additional clinical and multimorbidity information; however this is currently not permitted by the HPO. For this study, access to HIPE data was granted through Health Atlas Ireland (Appendix G) which is part of the Health Intelligence Unit of the HSE. Health Atlas Ireland provides an analytical and display window to a range of databases including demographic, hospital activity, mortality data, and provides a range of mapping functions. It is not possible to utilise this interface to analyse specific patient details or information, but instead consists of aggregated reports, based on the search criteria entered.

6.3.4. Clinical coding

Clinical coding is a specialised task performed by trained staff in hospitals nationwide. All personnel responsible for coding HIPE data were previously trained by the HIPE unit of the ESRI, and currently by the HPO. Irish Coding Standards (ICS) were developed to complement the Australian Coding Standards (ACS), and are revised regularly to reflect changes in clinical practice. The standards apply to activity coded in HIPE and provide guidance on all aspects of HIPE data collection in the Irish hospital setting. Training on coding is provided by the HPO and formally by the ESRI at beginner, intermediate and experienced levels. The work of new coders is closely monitored and follow-up training is provided at hospital level where patient's medical charts are available. Training is hospital-based for all levels to help coders with particular queries, difficult areas of coding and any issues experiences with data extraction, data coding or the use of the HIPE system.

When the patient is being discharged from hospital, or if the patient dies in hospital, the discharging clinician completes a discharge summary which is kept in the patient's medical chart. The hospital-level HIPE coder extracts the data related to the patient discharge (or death) and then inputs this information into the HIPE computer system. Data is validated at entry point and as well as on exported data.

6.3.5. International Classification of Disease (ICD)

The International Classification of Disease (ICD) is the standard diagnostic tool for epidemiology, health management and clinical purposes (available at www.who.int/classification/icd). ICD is the international standard for reporting diseases and health conditions and the foundation for the identification of health trends and statistics globally. This system allocates unique codes to all medical conditions and procedures. The ICD-10 Australian Modification (ICD-AM) is an alphanumerical

scheme which is structured by body system and aetiology and comprises of three-, four- and five-character categories. The ICD-10-AM consists of a tabular list of diseases and an accompanying index that has been modified in Australia by the National Centre for Classification of Health (NCCH) with assistance from clinicians and coders. Close links are maintained with the World Health Organisation (WHO) to ensure maintenance of international compatibility.

The Australian Classification of Health Interventions (ACHI) is a multifaceted classification which is structured by body system, site, procedure type, and consists of a list of procedures with an accompanying seven-digit index codes. The ACS is national standards which were developed by the NCCH to provide guidance on the application of ICD-10-AM and ACHI codes. Standards are categorised by site and or body system according to clinical speciality and to the disease or procedure with which it is related. The ICS were developed to guide coding in Ireland and to compliment the ACS. ICD-10-AM is based on the WHO international classification of diseases. Uses of the ICD include monitoring of prevalence and incidence of diseases and other health problems which provides evidence of general health condition of countries and populations. It also has a role in observing reimbursements, resource allocation and is also involved with safety and maintaining quality guidelines.

Ireland updates the clinical classification every four to five years to ensure that the classification is consistent with international use. ICD-9-CM was used in Ireland from 1999-2005. The ICD-10-AM 4th edition was introduced in Ireland for all discharges from the 1st of January 2005 to 31st of December 2008. Following this, the ICD-10-AM 6th edition was introduced from the 1st of January 2009 and continued until the 31st of December 2014. Ireland updated to the 8th edition of the ICD-10-AM/ACHI/ACS for all discharges from the 1st of January 2015, which continues today.

6.3.6. How HIPE data is generated and used

HIPE records patient discharges as 'episodes', with an 'episode' of care beginning at admission to hospital, as a day case or in-patient, and ending at discharge from (or death in) that hospital (and in a discharge record being created). Patients may be admitted to hospital more than once in any given time period with the same or different diagnoses. Therefore, in the absence of a unique patient health identifier, the data does not permit the analysis of certain data such as the number of hospital encounters per patient. HIPE data includes patients who attended the Emergency Department who were subsequently admitted to hospital. HIPE data does not report on emergency department visits who were not admitted to hospital, nor does it provide information on outpatient clinic attendance.

For each 'episode' of care where a patient is discharged from hospital and a HIPE report is created the following data is collected:

- **Administrative data:** Patient name (retained within the hospital), case reference number and hospital number, dates of admission / discharge, day-case indicator, admission type and source, discharge status and destination, General Medical Services status, medical card number (GMS patient number), admitting and discharge consultant (encrypted), intensive care and private care days, public care days (optional), infant admission weight (for neonates and low-weight infants), date of transfer to pre-discharge unit (optional), admission mode, waiting list indicator.
- **Demographic data:** Date of birth, sex, marital status and area of residence by county or country.
- **Clinical data:** Principal diagnosis and up to 19 secondary diagnoses, principal procedure and up to 19 secondary procedures.

6.3.7. Health Atlas: the user interface

Health Atlas Ireland is open-source software, which was created by Health Intelligence, HSE. Health Intelligence is knowledge management and supports decision making and population health. Health Atlas incorporates database and statistical components, including a number of analysis tools which are delivered over a web enabled browser. Access to this platform was granted by Health Intelligence Ireland (Appendix G)

6.4. Study rationale

Within Ireland, the epidemiology and socio-economic impact of chronic pancreatitis is unknown. Studies from other countries have reported increases in the prevalence, incidence and hospitalisation of chronic pancreatitis. Furthermore, previous work within our research group found that there was an increase in acute pancreatitis admissions in Ireland (43). A significant increase in hospital admissions over 8 year was attributed to *per capita* alcohol consumption rates at that time (43). Therefore, it is logical to hypothesise that there may be a similarly high and/or increasing prevalence of chronic pancreatitis in Ireland.

Documentation of the hospitalisation trends and prevalence of chronic pancreatitis in Ireland would be valuable to both clinicians and service planners. Patients with chronic pancreatitis have a number of health and socioeconomic difficulties related to their disease. A comprehensive study of chronic pancreatitis prevalence and hospital admission rates in Ireland is justified to plan services, inform guidelines, and facilitate the rational allocation of healthcare resources. All of these factors will contribute to improved patient care for chronic pancreatitis patients.

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6.4.1. Study hypothesis

The prevalence and disease-related hospital activity of chronic pancreatitis patients in Ireland is comparable to international data, and there is a measurable temporal increase in prevalence and hospitalisation rates.

6.4.1.1. Study objectives

- To retrospectively investigate trends in acute public hospital patient discharges in Ireland related to chronic pancreatitis for the years 2009-2013 using a national administrative healthcare database
- To analyse patient information related to chronic pancreatitis including; age, gender, marital status, admission type, diagnosis, procedures, length of stay, discharge status, and mortality
- To analyse temporal data and to ascertain if there was a change in prevalence over the 5-year study period
- To analyse geographical variation in chronic pancreatitis discharge rates in Ireland

6.5. Materials and methods

6.5.1. Study description

Employing a retrospective study design, the HIPE system was analysed to extract patient related information and activity for the years 2009-2013. Data on hospital discharges were obtained from the HIPE system, which was accessed through Health Atlas Ireland. Data were extracted using ICD-10 codes K86.0 and K86.1. These codes correspond to patients discharged with a diagnosis of 'alcohol-induced chronic pancreatitis' and 'other chronic pancreatitis' respectively, the latter including idiopathic,

genetic, hereditary and other contributing aetiologies. To interrogate the HIPE database and analyse the data, a number of steps were taken which are detailed below. This analysis took place during a five-month period from September 2014 to January 2015.

6.5.2. HIPE database enquiry

For the years 2009-2013 inclusive, 'total patient numbers', 'total discharges' and admission types (emergency / elective / day-case) were extracted.

- **'Total discharges'** included all hospital discharges in any given year; patients were counted for each separate inpatient stay. In the same year, if a patient was admitted to the same, or another, hospital with a different medical record number, this was counted as a new admission. Discharges were therefore used as a proxy measure of hospital admission.
- **'Total patients'** counted each patient in a given year only once, even if there were several admissions.

Data for age, gender, chronic pancreatitis aetiology, marital status, admission type, and in-hospital deaths were extracted. Age, gender and aetiology data, were obtained for 'total patients' and 'total discharges' separately.

6.5.3. Prevalence estimation

Using National census data for 2011 obtained from the Central Statistics Office (CSO, www.cso.ie), an estimated total chronic pancreatitis prevalence for Ireland per 100,000 population (total patients / total population *100,000) was calculated. This was computed for the whole country, and then separately for the 26 counties of the

Republic of Ireland using county population accessed from the CSO. Ulster was reported as the three counties within the Irish Republic (i.e. Donegal, Cavan and Monaghan), excluding the six counties of Northern Ireland. As patients' individual home addresses were captured through HIPE coding, discharges accurately reflected geographical distribution of patients, rather than hospital locations.

6.5.4. Patient data

Due to the nature of this study, patients with chronic pancreatitis who were 18 years or over were analysed. A number of paediatric cases of chronic pancreatitis were recovered; however childhood chronic pancreatitis hospital activity was beyond the remit of this study, and thus those patients were excluded.

6.5.5. Ethical approval

Ethical approval for this study was granted by the Tallaght University Hospital / St James's Hospital Joint Research Ethics Committee (AMNCH/SJH JREC REF 2015-03 List 11(2)) (Appendix B). As this study was observation and descriptive, utilising aggregate data, patients were not identifiable, and there were no perceived risks or ethical inferences. Permission to access to the HIPE data was granted by Health Atlas Ireland (Health Intelligence Unit of the Health Service Executive) (Appendix G)

6.5.6. Statistical analyses

Descriptive statistical analyses were performed and analyses were conducted using SPSS Version 22 (SPSS, Chicago, IL, USA, 2015). The Mann-Kendall trend non-parametric test was used to identify a trend in series, with the null hypothesis being that

there was no trend, and the three alternative hypotheses being a negative trend, non-null, or a positive trend. This test was used to determine if there was an increase in total patients or total discharges over the 5-year study period.

6.6. Results

6.6.1. Total discharges and prevalence

Between 2009 and 2013, there were 7,424,194 total discharges from acute Irish hospitals in Ireland, of which 4,098 (0.055%) had a diagnosis of chronic pancreatitis. During the study period, the yearly number of 'total patients' ranged from the lowest 530, to the highest 614 (in 2009 and 2011 respectively). Total discharges ranged from lowest 749 to highest 999 (in 2010 and 2013 respectively). Given the anomalous increase in discharges in 2013, contact was made with the HPO and a request was made for clarification, and the raw and identified data was examined. The HPO revealed in a private correspondence to the thesis author, that this increase was due to multiple day-case admissions for a single patient in one institution during that year. Therefore, excluding day-case discharges, 'total discharges' ranged from 612 in 2010 to highest 652 in 2012 (Table 6.1). There was no statistically significant increase or decrease in total patients or total discharges for chronic pancreatitis over the 5-year period

6.6.2. Estimated prevalence

Based on the administrative database 'total patient' numbers from 2009 to 2013, along with the 2011 census data for Ireland, the crudely estimated prevalence of chronic pancreatitis ranged from 11.6 per 100,000 population to 13.4 per 100,000 population (in 2009 and 2011 respectively).

6.6.3. Admission type

Most admissions across the 5-year period were classed as 'emergency non-readmission', with this admission type accounting for greater than two-thirds of all episodes (66.5%–72.1%) for each year, except one. ‘Emergency non-readmission’ was lower in 2013 at just over half of all admissions (54%) due to the unusually high haemodialysis day-case admissions that year (as detailed in Section 6.6.7).

Similarly, day-case hospital admissions accounted for 15-20% of all hospital admissions in each year except 2013, again explained by almost two-fold increase in day cases that year compared to previous years. Elective hospital admissions were in the minority; consistently less than 15% of all episodes (Table 6.1).

	2009	2010	2011	2012	2013
Total discharges	753	749	809	788	999
Total patients	530	548	614	576	601
Alcohol induced CP (K86.0)					
Total discharges	215	202	226	236	222
Total Patients	153	151	171	176	162
Other CP (K86.1)					
Total discharges	538	548	583	552	777
Total Patients	394	424	459	429	460
Estimated prevalence per 100,000	11.6	11.9	13.4	12.3	13.0
Admission type					
Emergency / in-patients	558	506	548	578	538
Day patients	112	137	160	136	387
Elective	83	104	92	72	71
Maternity	-	2	9	2	3
Sex					
Males, n (%)	514 (68.3)	533 (71.2)	547 (67.6)	553 (70.2)	550 (55.1)
Females, n (%)	239 (31.7)	216 (28.8)	262 (32.4)	235 (29.8)	449 (44.9)
Age Group					
Under 20 years, n (%)	16 (2)	14 (2)	12 (1)	24 (3)	29 (3)
20-44 years, n (%)	276 (37)	240 (32)	251 (31)	290 (37)	260 (26)
45-64 years, n (%)	340 (45)	351 (47)	385 (48)	337 (43)	565 (56)
65 years and over, n (%)	121 (16)	144 (19)	161 (20)	137 (17)	145 (15)
Marital / civil status					
Single	268	270	260	263	253
Married	230	210	246	222	222
Widowed	43	50	53	39	30
Other	94	74	76	88	80
Unknown	~	~	~	55	~
Divorced	~	~	~	28	8

Table 6.1: Number of acute public hospital discharges with chronic pancreatitis, including corresponding demographic data (2009-2013 inclusive)

Data presented as absolute patient numbers unless otherwise indicated

K86.1	2009	2010	2011	2012	2013
Total Discharges	547	557	583	552	763
Total Patients	401	432	459	429	450
Sum Bed Days	5154	4659	5475	4732	4248
Mean Bed Days	9.42	8.36	9.39	8.57	5.57
Median Bed Days	5.0	4.0	4.0	4.0	1.0
ICU Days (Sum)	280	211	370	259	198
Male	315	369	359	364	364
Female	196	188	224	188	339

K86.0	2009	2010	2011	2012	2013
Total Discharges	220	205	226	231	220
Total Patients	157	153	171	172	160
Sum Bed Days	2111	1974	2166	2138	2086
Mean Bed Days	9.6	9.63	9.58	9.26	9.48
Median Bed Days	5.0	5.0	5.0	5.0	5.0
ICU Days (Sum)	170	113	129	61	15
Male	174	174	188	185	177
Female	46	31	38	46	43

Table 6.2: Hospital discharges for K86.0 and K86.1 from 2009-2013 inclusive

6.6.4. Gender and age

For each year, males were in the majority, accounting consistently for more than 65% of patient activity, except for in 2013, when discharge rates were almost equal between males (55.1%) and females (44.9%). This is most likely explained by multiple day case admissions to one hospital for one female patient for haemodialysis treatment in 2013 which notably inflated discharge and gender percentages (private correspondence from HPO discussed in section 6.6.10) The greatest proportion of patients discharged were in the 40-64 year age group, and this group were consistently greater than half of the proportion of total discharges ranging from 58.4% in 2009 to 66.9% in 2013.

6.6.5. Alcohol-induced chronic pancreatitis

The numbers of 'total patient' alcohol-related chronic pancreatitis discharges were 153, 151, 171, 176, and 162 for the years 2009-2013 respectively (Table 6.3). This represents a 6% increase between 2009 and 2013; however, there was no overall increasing trend, and it did not reach statistical significance (P=0.436). The number of 'total discharges' for alcohol-related chronic pancreatitis were 215, 202, 226, 236, and 222 for the same 5-year period respectively, and there was similarly no significant increase over 5 years. There were between 3.8 and 4.9 times as many male as female discharges for alcohol-induced chronic pancreatitis during the 5-year study period.

6.6.6. 'Other' aetiology chronic pancreatitis

There were twice as many 'other aetiology' chronic pancreatitis patients as alcohol-aetiology patients over the study period. For this group, 'total patients' numbers were 394, 424, 459, 429 and 460, for the years 2009-2013 respectively (Table 6.3). Therefore, between 2009 and 2013 there was a 16.8% increase in total patients. Based

on the Mann-Kendall trend test, there was an increase in 'other aetiology' total patients over the 5-year study period, however this did not reach significance (correlation co-efficient 0.857, P=0.888). There was also an apparent increase in total discharges during the study period, from 538 in 2009 to 777 in 2013, accounting for an increase of 44% between 2009 and 2013. Analysis for this trend did reach statistical significance (P=0.002). (Table 6.4)

	2009	**2010**	**2011**	**2012**	**2013**	**2009-2013 % increase***	**P value**
Alcohol aetiology Total Patients	153	151	171	176	162	5.9	0.536
Alcohol aetiology Total discharges	215	202	226	236	222	33	0.167
Other aetiology Total Patients	394	424	459	429	460	16.8	0.888
Other aetiology Total discharges	538	548	583	552	777	44.4	0.002^

Table 6.3: Total patients and total discharge changes over 5 years for alcohol and other aetiology chronic pancreatitis

**Represents % change between 2009 and 2013*
#Mann-Kendall trend test over 5 years
^Significant P-value, correlation co-efficient 0.857

6.6.7. Age groups

Overall, the greatest proportion of patient discharges were in the 40-64 year age group and this age group were consistently greater than half the proportion of total discharges, ranging from 58.4% in 2009 to 66.9% in 2013. The second highest was the 20-44 year age group, with discharge percentages ranging from the lowest 26% (260)

in 2013 to highest 37% (290) in 2012. Those in the 65 year and older age group had discharges between 2009 and 2013 of lowest 15% (145) (2013) to highest 20% (161) (2011).

6.6.8. Marital / civil status

Regarding marital status, most of the chronic pancreatitis patients who were discharged during the study period were classed as 'single' with the numbers ranging from 253 (25.3% in 2013) to 270 (36.0% in 2010). The second largest proportion of patient discharges were reported as 'married' with figures ranging from 222 (28.2% in 2012) to 246 (30.4% in 2011).

6.6.9. Bed days

Total bed days during the five year study period were; 7,265 (2009), 6,633 (2010), 7,641 (2011), 6,870 (2012) and 6,334 (2013). The mean bed days each year were highest in 2009 at 19.02 days and this decreased to 15.05 by 2013. The median bed days each year ranged from 10 in 2009 to 6 in 2013. Intensive Care Unit (ICU) fluctuated throughout the 5 year study period from 450 (2009), 324 (2010), 499 (2011), 320 (2012) and reduced to 213 in 2013 (Table 6.4).

	2009	2010	2011	2012	2013
Total bed days					
K86.0	2111	1974	2166	2138	2086
K86.1	5154	4659	5475	4732	4248
Total	7265	6632	7641	6870	6334
Mean bed days					
K86.0	9.6	9.63	9.58	9.26	9.48
K86.1	9.42	8.36	9.39	8.57	5.57
Total	19.02	17.99	18.97	17.83	15.05
Median bed days					
K86.0	5.0	5.0	5.0	5.0	5.0
K86.1	5.0	4.0	4.0	4.0	1.0
Total					
ICU bed days					
K86.0	170	113	129	61	15
K86.1	280	211	370	259	198
Total	450	324	499	310	213

Table 6.4: Total bed days and ICU days (2009-2013 inclusive)

6.6.10. Geographical trends

Notable geographic variation was found in the study, with high pockets of patient activity in certain counties in Ireland. The counties with the overall highest 'patient discharges' per 100,000 population were; Sligo (47.4 in 2009, 32.1 in 2010), Donegal (27.93 in 2011), Mayo (29.2 in 2012), and Galway (93.73 in 2013). The counties of Ulster had the highest rate per 100,000 in three of the five study years (2009, 2010 and 2012) at 21.0, 22.7 and 21.0 per 100,000 of population respectively. The most north westerly county, Donegal, is the only county to feature each year among the top five highest discharge *per capita* counties, except for 2013 where the highest were Galway (93.7), Kilkenny (27.3) and Leitrim (25.1). Overall, during the 5-year study period, the counties in the northwest of Ireland appeared to have a disproportionately high rate of

patient discharges compared to other regions. This trend is highlighted in Table 6.5 below.

As previously identified in 6.6.3 there was a notable surge in the number of discharges observed from county Galway in 2013 to 93.7 (previously the rate was 16.4-20.75). In the absence of a unique patient identifier in HIPE, it is not possible to ascertain if it is a number of patient discharges or a recurrence of discharges for a single patient. Therefore, to investigate this abrupt increase (more than fourfold) the author requested clarification from the HPO regarding particular patient data. The author was informed in a personal correspondence from HPO that the increase in hospital discharges was the result of multiple discharges for one patient from a Galway hospital. This patient, who had a diagnosis of chronic pancreatitis, was receiving day-case care for haemodialysis and had multiple admissions and subsequent discharges which inflated the total discharges for chronic pancreatitis in that county and in that year.

County	Population	2009	2010	2011	2012	2013
Leinster	**2,504,814**	**15.73**	**15.65**	**18.28**	**18.17**	**19.24**
Dublin	1,273,069	16.89	18.22	21.29	21.52	21.92
Carlow	54,612	14.65	10.99	25.64	18.31	18.31
Kildare	210,312	9.03	9.03	12.84	10.46	18.54
Kilkenny	95,419	22.01	11.53	20.96	17.82	27.25
Laois	80,559	7.45	7.45	6.21	8.69	8.69
Longford	39,000	7.69	15.38	12.82	15.38	10.27
Louth	122,897	17.09	21.16	17.09	18.71	17.09
Meath	184,135	13.58	8.15	14.66	20.09	21.72
Offaly	76,787	9.13	7.82	18.26	13.04	9.13
Westmeath	86,164	20.89	17.41	22.05	18.57	16.25
Wexford	145,320	18.58	21.33	11.01	11.7	14.45
Wicklow	136,640	19.79	13.91	13.91	11.71	6.59
Munster	**1,246,088**	**15.41**	**16.61**	**16.37**	**11.96**	**11.63**
Clare	117,196	8.53	11.95	9.39	10.24	11.95
Cork	519,032	17.92	16.95	18.69	13.78	13.1
Kerry	145,502	10.1	8.93	9.62	2.75	5.5
Limerick	191,809	16.68	19.24	17.2	15.64	14.6
Tipperary	158,745	15.75	31.64	22.68	14.49	5.67
Waterford	113,795	14.06	16.7	11.42	7.9	15.82
Connacht	**542,547**	**20.83**	**16.59**	**16.59**	**19.91**	**53.82**
Galway	250,653	16.36	12.77	19.55	20.75	93.73
Leitrim	31,798	25.16	15.73	22.01	9.43	25.16
Mayo	130,638	17.61	16.07	13.01	29.2	17.61
Roscommon	64,065	15.61	17.17	15.61	20.29	15.61
Sligo	65,393	47.4	32.11	11.22	16.82	24.47
Ulster(part)	**294,803**	**21.03**	**22.72**	**17.64**	**21.03**	**18.3**
Cavan	73,183	19.13	6.83	2.73	22.23	12.3
Donegal	161,137	22.34	31.03	27.93	22.96	24.2
Monaghan	60,483	19.84	19.84	8.27	13.23	9.92

Table 6.5: Frequency of discharge activity (2009-2013) per capita, per county, with the counties recording the three highest activity levels in a particular year highlighted in red

County	Population	Pubs **	Pubs Per Capita	Off-Licences	Hotels	Wholesalers	Restaurants	Producers
Carlow-Kilkenny	145,659	288	19.8	99	19	12	63	2
Cavan-Monaghan	120,483	296	24.6	155	17	13	33	3
Clare	111,336	291	26.1	72	18	9	60	3
Cork-East	114,365	210	18.4	81	14	48*	62	16*
Cork North-Central	117,170	215	18.3	83	14	48*	64	16*
Cork North-West	86,593	160	18.5	62	11	48*	48	16*
Cork South-Central	117,952	217	18.4	84	14	48*	65	16*
Cork South-West	82,952	153	18.4	59	10	48	45	16
Donegal	152,358	365	24.0	133	40	12	77	2
Dublin Bay North	146,512	89	6.1	84	16	184*	97	10*
Dublin Bay-South	116,396	70	6.0	66	12	184*	77	10*
Dublin Central	89,030	54	6.1	51	9	184*	58	10*
Dublin Fingal	141,162	86	6.1	81	15	184*	93	10*
Dublin Mid-West	110,427	66	6.0	63	12	184*	72	10*
Dublin North-West	90,534	55	6.1	52	10	184*	60	10*
Dublin Rathdown	87,470	53	6.1	50	9	184*	58	10*
Dublin South Central	114,660	70	6.2	66	12	184*	76	10*
Dublin South West	144,908	88	6.1	84	15	184*	95	10*
Dublin West	113,179	69	6.1	65	12	184*	74	10*
Dún Laoghaire	118,791	72	6.1	68	13	184*	78	10*
Galway East	89,564	177	19.8	77	24	29*	53	6*
Galway West	150,874	298	19.8	128	41	29*	89	6*
Kerry	145,502	435	29.9	131	50	20	138	5
Kildare North	115,350	104	9.0	75	12	12*	48	4*
Kildare South	115,350	79	6.8	58	10	12*	37	4*
Laois	87,745	123	14.1	59	9	6	20	1
Limerick City	113,835	206	18.1	74	13	14*	47	2*
Limerick County	83,834	154	18.4	55	10	14*	35	2*
Longford-Westmeath	116,802	259	22.2	105	11	16	54	2
Louth	143,272	182	12.7	97	10	20	53	5
Mayo	120,332	273	22.7	112	40	7	76	3
Meath East	86,572	98	11.3	54	6	18*	32	3*
Meath West	85,550	97	11.3	54	6	18*	32	3*
Offaly	87,640	126	14.4	45	5	1	20	2
Roscommon-Galway	84,586	203	24.0	39	4	2	20	1
Sligo-Leitrim	119,153	254	21.3	77	16	10	36	4
Tipperary	147,801	422	29.0	120	17	16	49	8
Waterford	113,795	220	19.3	86	15	5	67	4
Wexford	145,320	265	18.2	108	22	15	73	6
Wicklow	141,012	151	10.7	87	18	14	72	6

Table 6.6: Alcohol availability in Ireland, based on data recorded by Ireland's drink and hospitality sector, and per electoral constituency

*Data source: The Drinks Industry Group of Ireland. *denotes within the county, not the constituency. ** Pubs per capita exclude other sources of alcohol attainment*

6.7. Discussion

6.7.1. Summary of the findings

This was the first study to examine activity trends and hospital discharges for chronic pancreatitis in Ireland, and remains one of a few studies conducted in Europe to date. The author has described the frequency of in-patient chronic pancreatitis discharges from all acute public hospitals in Ireland between 2009 and 2013, and has estimated a crude prevalence based on these data.

These data show that public hospital activity for chronic pancreatitis remained relatively the same during the five year study period. There was no apparent increase in total patients or total discharges for chronic pancreatitis between 2009 and 2013, nor was there a decrease. However, there was an increase in 'total patient' and 'total discharges' for the 'other-aetiology' chronic pancreatitis group (but not for the alcohol aetiology group). There were notable differences in regional activity for chronic pancreatitis patients.

6.7.2. Temporal changes in chronic pancreatitis activity

The results of the study showed that hospital discharges for chronic pancreatitis remained stable and changed minimally during the five year study period which is similar to other prominent studies (336, 337). Regarding Ireland, there have been no other data on chronic pancreatitis epidemiology for comparison; however a report on acute pancreatitis activity provides some context. O'Farrell *et al* (43) examined emergency hospital admissions for acute pancreatitis and reported a 54.1% increase in an 8 year period from 1997 to 2004. An increase in acute pancreatitis activity might feasibly result in an increase in chronic pancreatitis activity. However, as the present study examined data between 2009 and 2013, it is possible that the time lapse was too

short to measure the impact of increased acute pancreatitis activity on chronic pancreatitis activity. Another consideration is that admission rates for acute pancreatitis are likely to be higher, (since an episode of acute pancreatitis usually requires hospital admission, whereas patients with chronic pancreatitis may not). This presents a difficulty when comparing both diseases. Other studies have looked at temporal changes in hospital rates and activity for chronic pancreatitis, and have reported similar findings. The stationary activity for chronic pancreatitis observed in the present study was similar to results from a US study by Yang and colleagues (337). They examined epidemiological data on alcohol-related diseases including chronic pancreatitis between 1988 and 2004 in the US. The authors used a similar methodology of exact counts of patients using an inpatient register which is the largest representative sample of US hospitals. They found no change in discharge rates for chronic pancreatitis over 17 years. The authors (337) also reported that hospital discharges for acute pancreatitis were rising steadily, the reasons for which were unclear and seemed not to be related to a major shift in alcohol consumption. Yadav and colleagues (336) also reported relatively stable chronic pancreatitis activity and did not observe an increase or decrease in hospitalisation rates for chronic pancreatitis patients. Both of these US studies were comparable in the methodology of patient counts and in the time period studied, and are likely to represent true hospitalisation rates at population level.

In England and Wales (335), hospital discharges for chronic pancreatitis increased steadily between 1960 and 1988, with reported discharge rates of 8.3 (1960-4), 10.2 (1965-9), 10.8 (1970-4), 17.7 (1975-9) and 31.8 (1980-84) per million. There was a fourfold increase in chronic pancreatitis discharges amongst men, a twofold increase among women, and an upsurge in chronic pancreatitis-related deaths. The authors speculated that these increases might be related to a concurrent growth in annual *per capita* alcohol consumption at that time. The increases were mirrored in a second regional study from England which reported that the age-standardised hospital

admission rate for acute pancreatitis increased by 43%, whilst those for chronic pancreatitis doubled from 4.3 to 8.6 per 100,000 during the 10 year period between 1989/1990 and 1999/2000 (346).

A similar rise in hospital admissions over time has also been observed in Finland where the incidence of chronic pancreatitis discharges increased from 10.4 to 13.4 (an increase of 26%) between 1979 and 1989 (332). The incidence of pancreatitis in the whole population increased from 46.6 to 73.4 per 100,000 during this two-decade study period (332). There was a strong positive correlation between the incidence of pancreatitis discharges, the incidence of chronic pancreatitis discharges, and the consumption of alcohol in Finland (332). These data are remarkably consistent considering they were collected at different times, in different countries using dissimilar methodologies. Data were overall consistent with a steady increase in chronic pancreatitis activity in Finland over time.

In the Netherlands between 1992-2004 hospital discharges for acute pancreatitis increased substantially from 1,785 to 3,120 representing a 74.8% increase (146). Accordingly, a 75.4% increase from was noted for chronic pancreatitis during the same 12 year period (146). The overall annual incidence of chronic pancreatitis admissions rose from 5.2 to 8.5 per 100,000 (146). This study shows a substantial increase in both acute and chronic pancreatitis over a 12 year period with a higher rate observed in women than in men. After age and sex standardisation, the annual number for both acute and chronic pancreatitis increased by at least 50% (146). It is thought that this increase is in-line with earlier study from the Netherlands, which found that the incidence of first attack acute pancreatitis increased between 1985 and 1995 (321).

The increase in activity reported in earlier studies may have coincided with improvements in the diagnosis chronic pancreatitis. Some of the increases are also correlated with alcohol consumption in some select countries. It may also be that

patients do not present to hospital as frequently as before, perhaps due to better management at outpatient or community level, although there are no data to suggest or support this. If this is the case, we would not expect to observe a decrease in acute pancreatitis activity, due to its urgent nature.

6.7.3. Age and gender

The majority of the chronic pancreatitis discharges in Ireland were aged in the fourth to sixth decade. This was consistent with studies from Finland, France, Italy, and Belgium (143, 347-349) and therefore it seems that chronic pancreatitis is a 'disease of middle age'. Lankisch and colleagues described a peak incidence in men between 45 to 54 years and a small peak in incidence in women between 35 to 44 years and in this study men were in the majority of cases 88% (331). In France an overall peak incidence in patients with diagnosed or suspected chronic pancreatitis was observed between ages 45 to 49 years, and again the majority of patients were male (84%) (347). In the current study, females accounted for between 29% and 45% of all chronic pancreatitis patients. Whilst the proportion of men and women who develop acute pancreatitis are thought to be equal with no sex-related risk (86), chronic pancreatitis is known to occur more frequently in men. It is proposed that the higher proportion of male prevalence of chronic pancreatitis in many studies may be due to heavier drinking and smoking patterns in males when compared to females. However results from recent studies suggest that genetic factors also play an important role in this difference (274, 350, 351). Therefore chronic pancreatitis associated with alcohol-related aetiology is thought to be more common in males (141, 331, 352, 353), though gender-differences are thought to disappear with similar levels of alcohol consumption (273). The report of 45% female prevalence of chronic pancreatitis in the current study is important, and it is consistent with other studies which have documented increased prevalence of disease amongst women. Non-alcohol aetiology is thought to be more evenly

distributed in men and women, and it is postulated that chronic pancreatitis may be associated with non-alcohol aetiology in up to 70% of female cases (354). Chronic pancreatitis in females is thought more commonly to be related to gallstones, autoimmune disease or to be idiopathic (86).

However, the ratio of male to female in chronic pancreatitis is not static over time, or between countries. In England and Wales (335), chronic pancreatitis incidence was calculated using hospital episode statistics and diagnosis at discharge between years 1962 and 1985. In 1962, the annual incidence was 1.0 and 0.9 per 100,000 for males and female respectively. However, this increased fourfold for males (4.3) and only twofold for females (2.1) in 1985. The authors pointed towards improvements in diagnosis and imaging, but the reasons for changes in gender distribution were in fact unclear. In the Netherlands, Spanier and colleagues (146) used registry data to observe trends in hospital admissions for pancreatitis. They reported that whilst males with chronic pancreatitis were overrepresented throughout the study period (1992-2004), there was a higher increase in female hospital admissions than in male admissions (146). More recent epidemiological studies have suggested the prevalence of chronic pancreatitis amongst women is more common than previously believed (82, 336, 352, 355). One study reported that chronic pancreatitis incidence was increasing in women and decreasing in men when comparing two study periods: 1980-1984 and 2000-2004 (133). The authors used national registry data to explore diagnoses of first-time chronic pancreatitis in patients <30 years of age in Denmark. The authors report that the standardised incidence rate increased for women from 0.66 per 100,000 in the period 1980-84 to 0.89 per 100,000 in 2000-2004.

In summary, the age and gender rates described by the current study are generally consistent with the literature. Chronic pancreatitis appears to be predominantly diagnosed in men. However, many studies, and our own data included, point to a high and increasing rate of female gender amongst diagnoses of chronic pancreatitis.

6.7.4. Aetiology

There were more than twice as many 'other aetiology' chronic pancreatitis discharges as alcohol aetiology discharges in the present study. This is in contrast to the commonly held belief that most chronic pancreatitis is usually caused by excess alcohol consumption in Western countries. However, the findings of the current study are consistent with several recent large-scale studies.

Two recent large multicentre studies also reported a similar rate of non-alcohol aetiology, - one in Italy (353) which reported that 34% of patients had alcohol-related chronic pancreatitis between 2000 and 2005. In the US (354) 30.2% of patients had alcohol aetiology, and alcohol-related aetiology was found more commonly in black than in white patients (77% *vs* 42%). Interestingly, the low prevalence of alcohol aetiology found in Italian patients was much lower than the 74-79% alcohol-related disease reported between 1971 and 1995 (352, 356). Both of these studies reported that chronic pancreatitis caused by alcohol and tobacco was more common in males, while idiopathic, obstructive and autoimmunity-related aetiologies were more common in females (353, 354). There does appear to be a gender difference regarding aetiology. In another large American epidemiological study, alcohol aetiology was found more frequently in men than in women (59.4% and 28.1%) respectively, but non-alcohol (18% men, 36.7% women) and idiopathic aetiologies (22.6% men, 35.2% women) were more frequent in women (355). In Europe, Capurso and colleagues (329) also reported a low rate of alcohol aetiology (25%) which was mirrored in findings from

Denmark (133). The NAPS2 (a multicentre consortium of 20 US centres), similarly reported lower-than-expected alcohol aetiology in its cohort, with only 38.4% of men and 11% of women with chronic pancreatitis being heavy drinkers (94). Therefore, these studies, (all of which were published in the last 20 years), were in agreement with the data from Ireland.

However, other notable studies have reported that the majority of chronic pancreatitis diagnoses are alcohol-related, and are correlated with *per capita* heavy drinking. In 2002, Lankisch *et al* ascribed an alcohol aetiology to 72% of patients with chronic pancreatitis (331), which was attributed to very heavy drinking patterns amongst German patients. And in Spain, a survey of specialist pancreatic units, found that three out of every four patients had an alcohol aetiology (328). The authors suggested that the presence of obvious risk factors (such as heavy drinking and smoking), results in raised clinical suspicion for chronic pancreatitis. This may have the benefit of leading to a quicker diagnosis, while patients who do not smoke or drink may be subject to a delay regarding a firm chronic pancreatitis diagnosis.

The finding of a lower prevalence of alcohol-aetiology chronic pancreatitis among this cohort is perhaps surprising considering the known culture of heavy drinking in Ireland, however overall this observation is not completely unexpected. There has been a greater understanding of the disease in recent years, along with increased understanding of the various aetiologies. In recent years, the risk of pancreatitis associated genetic mutations of *SPINK1*, *PRSS1*, and *CFTR* mutations has been increasingly well established, and testing for genetic associations is being considered in clinical practice, especially in those with unexplained disease (101).

It is possible that some patients are misclassified as having alcohol-related chronic pancreatitis. In Italy (353) 10% of patients labelled as having alcohol-related chronic pancreatitis reportedly drank less than 80g of alcohol per day, while patients who were diagnosed as obstructive aetiology, reportedly consumed more than 80g of alcohol per

day. In a large multicentre American study, only 38% of men and 11% of women with chronic pancreatitis were heavy drinkers (94). Therefore, it is plausible that earlier epidemiological studies, where the majority were labelled as alcohol-pathology, and in the absence of other known causes, patients may have been subject to some level of misclassification.

6.7.4.1. The reasons for lower alcohol aetiology in Ireland

Despite the relatively low alcohol-induced chronic pancreatitis aetiology described in recent worldwide studies (94, 273), the proportion of alcohol-induced chronic pancreatitis in the current study fell at the lower end of this scale. This is perhaps surprising, as Ireland is known to be among the highest consumers of alcohol, at least anecdotally, and the frequency of chronic pancreatitis is thought to correlate with *per capita* alcohol consumption (332, 335).

In fact, Ireland has the fourth highest level of alcohol consumption in the Organisation for Economic Cooperation and Development (OECD) region, and the second highest rate of binge drinking in the world (357). Alcohol consumption increased significantly in Ireland between 1980 (4.9 litres per person) and 2001 (14.3 litres per person), however it has since decreased. In 2012 in Ireland the average *per capita* consumption was 11.6, which fell to 11 litres in 2014 and again slightly decreased to 10.53 litres in 2015 (357). However, although there may be year-to-year fluctuations, the average consumption of alcohol in Ireland remains above the OECD average.

It appears that alcohol-related hospital activity may too be decreasing. A recent study in Ireland (358) reported a 30% decrease in alcohol-related admissions to one intensive care unit in Ireland in 2013 compared to 2008, but the reasons for this were unknown and not immediately obvious. The authors suggested a number of potential explanations for this, including a reduction in youth binge drinking reported in one Irish

study (359), and potentially increased public awareness about the dangers of excessive alcohol consumption. The HIPE database does not provide details on 'other' aetiologies. Therefore, it is difficult to estimate if the low alcohol-related chronic pancreatitis prevalence is due to a decline in recent decades in alcohol consumption, or, if it is related to a previous overestimation of alcohol related disease. Equally, it is not known if the higher proportion of 'other aetiologies' is due to high numbers of idiopathic, genetic or other causes. In fact, the diagnosis of chronic pancreatitis is not straightforward, and in particular it may be difficult to ascertain if chronic pancreatitis is due to alcohol-excess. The relationship between alcohol consumption and chronic pancreatitis is complex and dose-dependent, and is affected by other factors (for example, smoking). Therefore in the absence of reliable information on individual alcohol consumption, the aetiological accuracy should be viewed cautiously. Prior data from our unit (43) highlighted an increase in acute pancreatitis hospital admissions between 1997 and 2004. There was also a 10-fold increase in female admissions aged 20-29 years specifically for alcohol-related acute pancreatitis from 2001, albeit from a low base. Therefore, a corresponding increase in alcohol-related chronic pancreatitis admissions could be expected. However, it may be that any increase in chronic pancreatitis would take longer to manifest.

6.7.5. Estimating the prevalence of chronic pancreatitis in Ireland

The estimated prevalence of chronic pancreatitis from this study, measured by hospital discharges, was between 11.6 and 13.4 per 100,000 over a five-year period. This estimation was crude and is likely to be a gross underestimation. This may be in part due to the inherent limitations of administrative databases such as HIPE, including problems around accurate coding. Furthermore, this estimate relies on hospital discharges only, therefore, only accounting for cases that presented and were admitted to hospital during the data collection period. HIPE does not record outpatient visits,

emergency department visits without admission, nor does it record primary care data. There are undoubtedly many chronic pancreatitis patients who attend GP and outpatient clinics for management, and are therefore not accounted for in hospital-based publications worldwide. Part B of this chapter describes a systematic review of the international studies reporting incidence and prevalence for chronic pancreatitis.

6.7.6. Geographical variation

Notable geographical variance was found in the study, with high pockets of patient activity for chronic pancreatitis in specific areas of Ireland. In particular, there was a high prevalence of chronic pancreatitis in western and north-western counties, specifically; Sligo, Mayo, Donegal and Galway. In this section the four possible explanations for this geographical bias for the North West of the country will be explored; specifically alcohol consumption, cystic-fibrosis prevalence, social deprivation, and inequality in access to primary care.

6.7.6.1. Alcohol consumption

The occurrence of chronic pancreatitis is definitively correlated with excess alcohol consumption (86, 273) and therefore it is feasible that epidemiological trends for chronic pancreatitis may be associated with data on alcohol consumption. This has been demonstrated in several other countries. A recent European Union-wide study found a positive association between deaths from pancreatitis and *per capita* consumption of alcohol, with consistent results emerging across 14 western countries (44). Díte and colleagues also found geographical differences in incidence in South and Central Moravia in the Czech Republic, and speculated that this could be attributed to regional variances in alcohol consumption (333). Therefore, the geographical variations in chronic pancreatitis prevalence in Ireland could conceivably have parallels

to regional variations in alcohol consumption. Each year, the top three counties with the overall highest patient discharges per 100,000 were Sligo, Donegal, Mayo, Galway, Tipperary, Leitrim, Kilkenny, Galway and Carlow. Donegal featured in the highest top three prevalence figures, for four consecutive years (Table 6.5).

To quantify if there was an association between prevalence rates and alcohol consumption, the thesis author accessed alcohol data from The Drinks Industry Group of Ireland (360) (Table 6.6). These data are reported by electoral constituency, and *per capita* public house (pub) data, and are estimated using each constituency's population. In Ireland the highest number of pubs is in county Kerry which has 435 pubs for its 145,502 population and 29.9 pubs *per capita*. The second highest was county Tipperary with 29.0, followed by Clare (26.1), Cavan-Monaghan (24.6), Donegal (24.0), Mayo (22.7), Longford-Westmeath (22.2) and Galway East/West and Carlow-Kilkenny with 19.8 per 100,000. These data are estimated using numbers of pubs only; however, there are a number of other methods to source alcohol including off-licences, restaurants and wholesalers. Notably, some counties with high pockets of chronic pancreatitis activity also have high *per capita* of pubs and these include Tipperary, Donegal, Mayo, Galway, and Carlow-Kilkenny (Table 6.6). It is plausible that there is a link between alcohol availability / access, alcohol drinking, and chronic pancreatitis in these counties; however these data do not provide definitive evidence of this. While national *per capita* alcohol consumption is declining, alcohol consumption nationally remains a concern, and remains above the OECD average (357). A recent report from the Health Research Board (HRB) (361), found that the number of alcohol related discharges increased by 82% from 9,420 in 1995 to 17,120 in 2013, with males accounting for 72.4% of discharges. In 2013, alcohol-related discharges in Ireland accounted for 160,211 bed days, equivalent to 439 beds daily (361).

6.7.6.2. Cystic fibrosis prevalence

To further explore the high activity in the northwest of Ireland, the author speculated that there might be a concurrent high prevalence of cystic fibrosis in those same regions. Ireland has the highest prevalence of cystic fibrosis in Europe (250), therefore there may be regional differences in the prevalence of cystic fibrosis-related gene carriers that account for regional variation in the prevalence of chronic pancreatitis. However, data from the Cystic Fibrosis Registry of Ireland show that the counties with the highest occurrence of cystic fibrosis over the study years were mostly in the south and south west of the country, namely Clare, Kerry, Limerick and Tipperary. County Wicklow had the highest prevalence of cystic fibrosis of 41.57 per 100,000. Therefore, the regional variations in cystic fibrosis are dissimilar to that of chronic pancreatitis.

6.7.6.3. Social deprivation

Thirdly, it was theorised that the counties with high chronic pancreatitis activity were more socially deprived. However, the available national deprivation data (362) were not amenable to making such comparisons. Therefore, geographical anomalies in prevalence, presumed to be associated with social deprivation in specific counties in Ireland, were not quantifiable. It may be worthwhile in future research efforts to determine if inter-county deprivation or rurality is a co-factor on higher prevalence chronic pancreatitis discharges in specific counties.

6.7.6.4. Inequality in primary care

Chronic pancreatitis is a chronic condition and in general, aside from symptomatic flare ups which require hospitalisation, chronic diseases are best managed in the primary

care (284) community and outpatient settings. Therefore, a fourth explanation for the geographical variation in discharges for chronic pancreatitis could be uneven primary care resourcing within Ireland. Geographical variation in hospitalisation rates may reflect differences in the availability of services which reduce the need for hospitalisation, such as primary care. There is substantial regional variation in the number of GPs per 100,000, indicating that there may be both regional and national disparity in supply and demand (363). Two recent systematic reviews reported an association between hospitalisation for ambulatory care sensitive conditions (such as diabetes), and GP population ratio and primary care resourcing (364, 365). Rates of hospitalisations for ambulatory care sensitive conditions are considered as an important indicator of health service performance. It is plausible that in areas with substandard access to GP or lack of chronic care management, there may be increased hospital admissions to treat complications which could potentially be managed in primary care. While it is feasible that imbalanced primary care resourcing may therefore affect hospitalisation rates for chronic pancreatitis, there are no data to support this assertion at present. This area of chronic pancreatitis management constitutes a critical research gap.

6.7.7. The use of HIPE in Ireland

This study provided crucial data on the epidemiology of chronic pancreatitis in Ireland using information extracted from the HIPE database. HIPE is a valuable information source that has widespread use for research and planning, and provides data publishable in academic journals and reports. However, as with all administrative databases, HIPE is not without its limitations. The quality of data produced by HIPE has previously been questioned (366, 367). Furthermore, suggestions for HIPE data improvement have been made (368). Nevertheless, these limitations may stem from a

historical reluctance of clinicians to engage meaningfully with HIPE, along with misunderstandings of the capacity, intended purpose, and scope of the database (369). Wiley *et al* (369) argued that while there are operational deficiencies with the HIPE system, these should not detract from the recent significant improvements to the system. Notwithstanding the potential issues around data validity and operational inconsistencies (which occur in all administrative databases), HIPE is an important and useful research tool which has been used for many valuable studies.

In fact there have been two studies investigating the reliability of HIPE-derived data in Ireland. Buckley and colleagues (370) conducted a study to assess the reliability of routine hospital discharge data to determine the level of agreement between hospital discharge data and medical records for lower extremity amputation and diagnosis of diabetes. A high level of agreement was reported between both data sources, and the authors suggested that HIPE is a sufficiently reliable tool for monitoring trends in this defined study area. A study by Moloney and colleagues (371) also supports these findings. The authors investigated differences between hospital consultants in terms of patient length of stay, re-admission rates, resource utilisation and diagnostic coding in one large teaching hospital in Dublin. It was reported that HIPE was very powerful in predicting differences in all of the outcomes studied. Thus, HIPE appears to be a reliable, powerful, and valuable resource for conducting research on hospitalisation in Ireland.

6.7.7.1. Benefits of HIPE

The positive aspects of the HIPE system include the 100% inclusion of acute public hospitals in Ireland, ensuring that the database contains the most comprehensive data for chronic pancreatitis currently available. The database was designed to collect information on hospital discharges treated in the inpatient setting. This system could

potentially expand to include the emergency department, outpatient and community setting data, and this deserves consideration, however; that is not currently the intended purpose. Furthermore, administrative databases (such as HIPE) are an easily-accessible source of large-scale disease-specific data, often at national level, which is of particular value for less common disease such as chronic pancreatitis. They have the essential benefit of being non-intrusive from a patient standpoint, and avoid the pitfall of recall bias. Administrative data collection is significantly less expensive, provides wider patient coverage, and is considerably more time-efficient than conducting prospective studies and trials. The coding system is modified intermittently to improve consistency and precision. Therefore, administrative databases such as HIPE can be used to plan health services and to guide policy decisions for the management of people with chronic diseases.

6.7.8. Limitations of HIPE

Like all administrative databases, HIPE has several important limitations. Draw-backs include problems around data quality, specifically miscoding or incomplete coding. For example, the primary diagnosis may be recorded, but other secondary diagnoses or co-morbidities may be excluded, and the analyst is unable to determine if a secondary diagnosis is absent, or just not recorded (372). In the present study, it is acknowledged that the data do not include all patients with chronic pancreatitis in Ireland, as it excludes outpatient data, emergency department visits excluding admission, and only patients who were hospitalised during the study period were included. Therefore, a large proportion of patients with chronic pancreatitis who did not present to hospital are potentially not visible to this epidemiological study. Therefore, these data represent ‘hospital prevalence’, rather than national prevalence for Ireland. However, not all hospital activity is accessible. Only patients that were actually admitted to hospital are

included, - and emergency room visits are not captured. This represents a considerable reason for underestimation of activity, as not all hospital visits result in admission. Private hospitals are also excluded, further limiting the coverage of the findings. Moreover, there is no unique patient identifier, - and therefore a differentiation or isolation of specific patient cases was not possible, limiting the investigation of potential disease comorbidities. Individual level study was not possible due to restrictions in accessing raw data containing patient information; therefore, data are aggregate. There were no clinical or pathological data available, and data are based on diagnostic coding from medical records. It was not possible to ascertain information on comorbidity, patient history, smoking and alcohol use, and therefore it is not possible to comment of the effect of these on the epidemiology of the disease.

6.8. Study limitations and strengths

6.8.1. Study limitations

In addition to the limitations described earlier, there are other considerations. This was a retrospective study, and it is based on trends, not patient cases. Therefore, a comparison using a defined cohort and matched controls was not possible. This study relied on routinely recorded data that limits data accuracy and completeness. This is somewhat restrictive and confines the analysis to the data contained on the database alone. The lack of a unique patient identifier is a definite limitation of this healthcare database, and this should be overcome to increase the accuracy of patient, disease and cost estimates. The HIPE database does not contain any clinical or pathological data and is solely based on diagnostic coding from medical records. Therefore, it is not possible to fully ascertain the role of environmental factors such as alcohol, smoking, comorbidity, or genetic factors and patient history on the disease epidemiology.

Finally, a five year study period was arguably too short to observe a difference in hospitalisation and epidemiological trends.

6.8.2. Study strengths

Notwithstanding the limitations, this study has notable strengths. This study is the first of its kind to publish data on chronic pancreatitis epidemiology and aetiology in Ireland. This opens the gateway to further extensive research, which may help in the planning and provision of services for patients. This study identified a lower alcohol-related aetiology than would be expected, therefore highlighting the role of other aetiologies in the pathogenesis of chronic pancreatitis.

6.9. Conclusion

In conclusion, this study represents the first nationwide study on hospital discharges for chronic pancreatitis. The reported estimated prevalence of 11.6-13.0 per 100,000 of population was similar to other studies worldwide utilising similar methodologies such as patient database or disease registry. The number of patients and discharges for chronic pancreatitis remained steady throughout the study period. Unexpectedly, there was double the number of 'other aetiology' chronic pancreatitis hospital discharges, compared with alcohol aetiology. Demographic characteristics such as age and gender were similar to that reported elsewhere. There were regional variations in chronic pancreatitis activity that could not be easily explained by geographical differences in alcohol consumptions, cystic fibrosis prevalence, social deprivation or general practice access. These results represent valuable prevalence and hospital activity data for a disease about which relatively little is known. It adds to a small, but important, body of

literature which will allow clinicians and policy makers to make rational decisions regarding allocation of resources and service planning for chronic pancreatitis in Ireland and internationally.

To further strengthen this work, Part B of this chapter describes a systematic search of the epidemiological studies on chronic pancreatitis. This study aimed to systematically explore the studies conducted on this topic internationally, and provides insight into the sizeable variations on prevalence worldwide.

6.10. PART B: a systematic review of the international prevalence and incidence of chronic pancreatitis

6.10.1. Introduction

As presented in part A of this chapter, there are heterogeneous published studies on the prevalence and incidence of chronic pancreatitis worldwide with variable results, and this has led to a degree of uncertainty regarding the true epidemiology of this disease. To address this ambiguity, and to clarify understanding of the inter-study variation in reported data, a systematic search of published literature was conducted.

The broad aim of this study was to determine the prevalence, incidence and hospitalisation of chronic pancreatitis worldwide. The specific objectives were;

- To identify if differences exist in the reported prevalence, incidence and hospitalisation of chronic pancreatitis worldwide
- To explore potential reasons for differences between different countries
- To compare and contrast data collection methodologies used to estimate chronic pancreatitis epidemiology
- To identify methods which may be used for future epidemiological estimates in chronic pancreatitis

6.10.2. Methods

6.10.2.1. Criteria for consideration of studies

The following study types were considered for inclusion; studies on the prevalence, incidence and hospitalisation of chronic pancreatitis, including surveys, observational studies, descriptive studies, registry data, and any studies reporting a population based estimates of chronic pancreatitis. Chronic pancreatitis patients were not limited by

aetiology, sex, and were required to have a diagnosis of chronic pancreatitis. Studies were limited to adults only (>18 years), but studies that included both adults and children were not excluded where adult data could be extracted. Only English language studies were included. No date restrictions were employed, but searches were restricted to human studies only. Single institution prevalence estimates or reports and regional studies were included.

6.10.3. Search details

The following bibliographic databases were searched for studies on chronic pancreatitis prevalence, incidence and hospitalisation

- NCBI National Library of Medicine (PubMed) (1946 to end June 2016)
- Elsevier Embase (1980 to end June 2016)
- Sciverse Scopus (1966 to end of June 2016)

The searches were conducted during June 2016 and search updates were created to automatically send updates of any potential literature to the authors from the aforementioned databases. The final date considered for inclusion of published work was the 31st of June 2016. The systematic search was assisted and guided by a medical librarian (DMcN) based in Trinity College Dublin. The author was further supported in developing and refining the search terms by a trained medical librarian (JMcM) at the Trinity Centre for Health Sciences, Tallaght Hospital. Both the librarian and thesis author were unblinded, that is, there were no restrictions on authors or journal names. The search strategy was set up for PubMed and then translated for use on EMBASE and Scopus. The search strategy was set up to search for articles with combinations of subject headings, key words (Boolean operands 'chronic pancreatitis, prevalence, incidence, hospital discharge, hospital admission, epidemiology, administrative database, time trends, hospital episode'.) Literature was also retrieved

through hand searching, secondary review of reference lists for studies not found through the electronic search of databases, and searches of conference proceedings and grey literature which was conducted by the thesis author and the medical librarian (DMcN). The titles and abstracts were reviewed by the author and the medical librarian (DMcN).

6.10.4. Study selection

Study abstracts were reviewed and appraised, and the full texts of potentially relevant papers were retrieved. The selection criteria were applied to suitable studies. Conference proceedings were considered for inclusion if they met the criteria and also had sufficient data and information available for review. For all studies included in the search, where there was missing data or requirement for clarification, the study author was contacted by e-mail.

6.11. Results

6.11.1. Search Results

The search of literature and selection process is summarised graphically in Figure 6.1. Manual searches of bibliographies and reference lists and hand searching and conference proceedings yielded 9 additional studies.

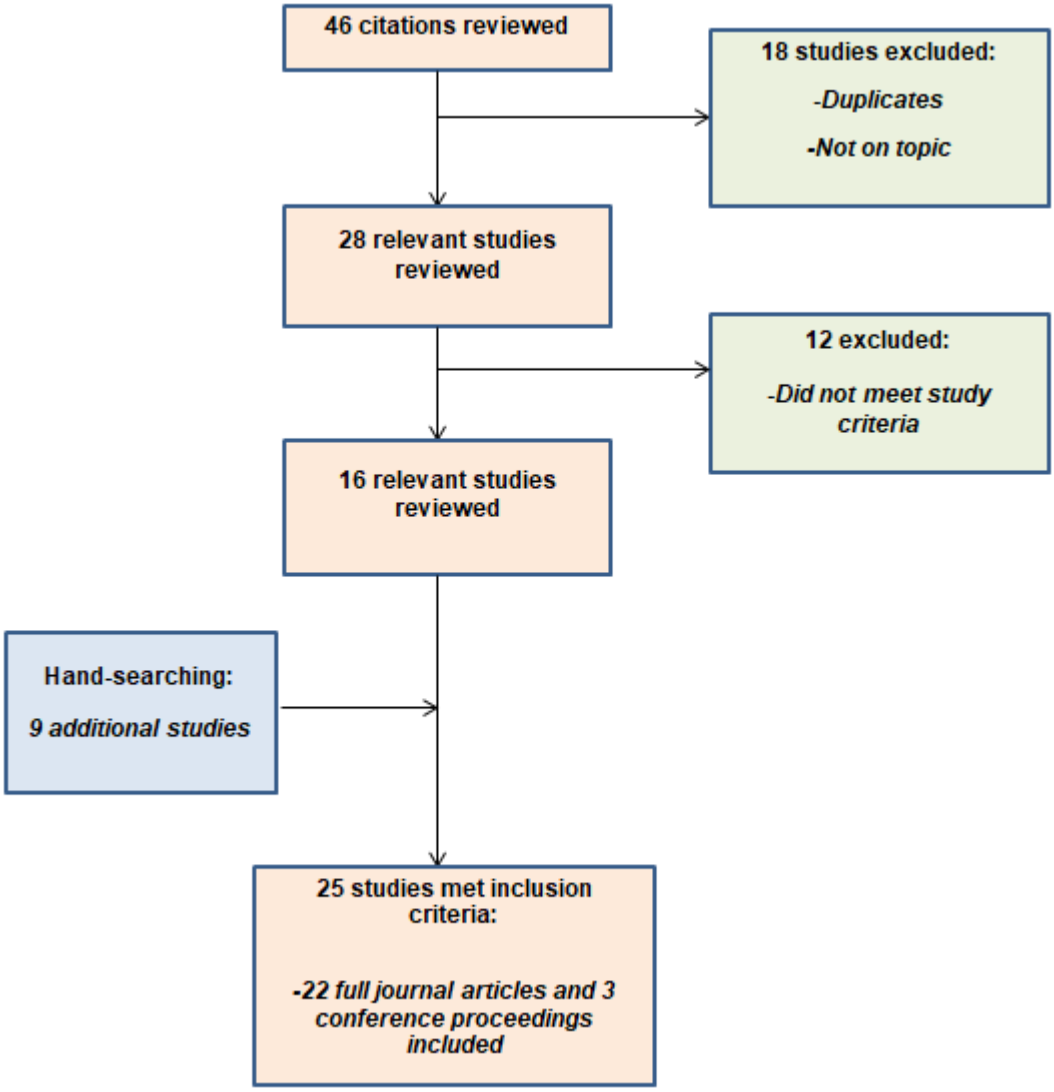

Figure 6.1: Flow diagram for the assessment of studies identified in the systematic review

6.11.2. Summary of studies included

Twenty-five studies met the required inclusion criteria and were included in the prevalence, incidence, and hospitalisation estimate for chronic pancreatitis worldwide (41, 45, 82, 95, 133, 135-139, 142, 144, 326, 328, 329, 331-336, 347, 373-375). The studies included were 22 full articles and three conference abstracts. Of these studies, 19 included chronic pancreatitis patients, one included both chronic and acute pancreatitis patients, one included alcohol chronic pancreatitis only, and four did not

identify the exact pancreatitis patient type. Six of the studies reported on prevalence, eight reported both prevalence and incidence, two reported incidence and four reported on hospitalisations. Thirteen of the studies were conducted in Europe, six in the US and six in Asia. Of the 25 studies, almost half (11/25) were published between 2000 and 2009, while 9 studies were published between 2010 and 2016. Of the remaining studies, one was published in 1972, one in 1982, and three from 1990-1993. These 25 studies included data from between 1940 and 2016.

6.11.3. Summary of methodologies

There were several variations in data collection methods used throughout the studies. Nine studies used methodologies such as registries / national database or hospital discharges to estimate incidence or prevalence. Two studies used registry data (133, 142), five used national databases or healthcare cost data (45, 336, 346, 373, 374), and two used hospital discharge data (143, 335). Ten of the studies used surveys to collect data (134-139, 141, 326, 329, 347). Three (3/10) of these were surveys of specialists or pancreatic hospital units reporting prevalence and incidence of chronic pancreatitis (327). One of the surveys was of primary care physicians to estimate prevalence of chronic pancreatitis (329). One of these studies estimated the prevalence of pancreatitis among alcohol disorder patients in one detoxification unit of 1,409 patients (95). One study utilised a healthcare cost dataset (336) containing 988 patients (329). Five of the studies employed retrospective, chart reviews and single institution patient records, with small numbers of patients ranging from 106 to 1,409 patients (82, 95, 144, 331, 334).

6.11.4. Prevalence

Thirteen studies worldwide have estimated the prevalence of chronic pancreatitis. In Europe, prevalence rates varied from 11.7–17.0 per 100,000 in Denmark (133), 24.9 in France (347), to 49.3 per 100,000 in Spain (328). The prevalence in a primary care survey in Italy was 30.2 per 100,000 (329). A multicentre study from China (139) found prevalence rates increased yearly over a 10 year period from 3.08 in 1996 to 13.5 per 100,000 in 2003. In Japan, the prevalence of chronic pancreatitis varied from 28.5 per 100,000 to 52.4 per 100,000 in a series of studies published between 1994 and 2014 (135-138). The prevalence of chronic pancreatitis varied according to the data collection method used. For example, studies using registry data or national databases reported prevalence of 11.7–17.0 per 100,000 (133). Surveys that included patient details and clinical information ranged from 3.08 to 52.4 per 100,000 (135-139). Surveys of specialist units and primary care estimating caseload ranged from 17.0 to 114-200 per 100,000 (134, 141, 326, 329, 347) (Table 6.7).

6.11.5. Incidence

The incidence of chronic pancreatitis has been reported 14 times worldwide, and similarly is varied throughout the studies, depending on data collection methodologies. The overall incidence of chronic pancreatitis was reported to be 1.8 per 100,000 in the Netherlands (142). In the UK (145) the incidence was 2.1 for females and 4.3 for males, while in other areas of Europe it ranged from 5.0 (326) to 13.4 per 100,000 (332). In the US, incidence ranged from 4.0 (336) to 14.9 per 100,000 (144). In Asia, the incidence ranged from 5.4 (136) to 14.4 per 100,000 (135).

6.11.6. Hospitalisation

Hospitalisation rates for chronic pancreatitis doubled in England (346), with age-standardised rates for chronic pancreatitis increasing by 100% from 4.3 per 100,000 in 1989/1990 to 8.6 per 100,000 in 1999/2000 (346). The age-standardised rates were consistently higher for males, with male-female ratios of 2:6 for chronic pancreatitis in 1999/2000. In earlier work from the UK (335), a four-fold rise in hospital discharges over a 25 year period from 8.3 per million per year in 1960-65 to 31.8 million per year in 1980-1984. A study from The Netherlands reported a 74.5% increase in hospitalisations between 1992 and 2004 (45), and the overall annual number of chronic pancreatitis admissions increased from 5.2 to 8.5 per 100,000 person-years. A study from one US state reported a hospitalisation rate of 7.75 per 100,000 (336). One US study (338) reported a decrease in admission rates from 8 to 4.5 per 100,000 (373) over a 5 year period, while another (339), identified a decrease in total chronic pancreatitis patient numbers, from 24,701 to 19,809 over an eight year period from 2002-2010. Unfortunately only conference abstracts for both of these studies were available and therefore clarification of study methodologies, or potential reasons for the decline, were not presented. Attempts to contact the authors for further clarifications were not successful.

Continent	Author, publication year	Country (region where applicable)	Year(s) studied	Study type***	Patient type	Prevalence	Incidence	Hospitalisation
Europe	(Current study) Ní Chonchubhair	Ireland	2009-2013	Hospital in-patient enquiry (national hospital discharges)	CP	11.6-13.4 per 100,000		
	Capurso *et al*, 2016 (conference abstract)	Italy	2016	Survey of primary care	CP	30.2 per 100,000		**-**
	Dzieniszewski & Jarosz, 1990	Poland (Warsaw)	1982-1987	Hospital survey	CP	17.0 per 100,000	5.0 / 100,000	-
	Jaakola & Nordback, 1993	Finland	1970-1980	Hospital discharges			13.4 per 100,000	
	Lévy, 2006	France	2006	Survey of gastroenterologists	CP	26.4 per 100,000	7.7	-
	Dite, 2001	Czech Republic	1999				7.9 per 100,000	
	Dominguez-Munoz, 2014	Spain	2014	Survey of specialists	CP	49.3 per 105,000		-
	Joergensen, 2009	Denmark	1980-2004	Registry	CP	11.7 – 17.0 per 100,000		-
	Andersen, 1982	Denmark	1970-75 1975-79	Retrospective study	ACP		6.9-10.0 per 100,000	
	Lankisch, 2002	Germany	1988-1995	Patient records	CP		6.4 per 100,000	
	Tinto, 2002	England	1989/90 – 1999/2000	Hospital episode statistics	CP	-		4.3 (1989/1990) to 8.6 (1999/2000) per 100,000 (100% increase for CP)
	Spanier, 2008	Netherlands	1992-2004	National database	CP	-		Admission rate 8.5 per 100,000 (75.4% increase)
	Spanier, 2013	Netherlands	2000-2005	Registry / linked cohort	CP		1.8	
	Johnson & Hosking, 1991	United Kingdom	1960-1984	Hospital discharge records			4.3 (male) 2.1 (female) / 100,000	
United States	Yadav, 2011	USA (Olmsted Co)	2011	Medical diagnostic index	CP	41.8 per 100,000	4 per 100,00	-
	O' Sullivan, 1972	USA (Rochester)	1940-1969	Patient records			8.7-14.9 per 100,000	
	Yadav, 2011	USA (Pennsylvania)	1996-2005	Healthcare cost dataset	CP	-		Rate: 7.75 per 100,000
	Yadav, 2007	USA	2002-2003	Chart review and	Pancreatitis	3% (of 1409)		-

				medical diagnostic index				
	Garg, 2015 (conference abstract)	USA	1997-2012	National database	CP	-		Admissions decreased from 8 to 4.5 per 100,000
	Shastri, 2014 (conference abstract)	USA	2002-2010	National database	CP	-		Admissions decreased from 24,701 to 19,809
Asia	Wang, 2009	China	1996-2003	Survey	CP	3.08 to 13.52 per 100,000		-
	Lin, 2000	Japan	1994	Survey	CP	28.5 per 100,000	5.4 / 100,000	
	Otsuki, 2005	Japan	2002	Survey	CP	35.5 per 100,000	14.4 / 100,000	
	Hirota, 2012	Japan	2007	Large-scale nationwide survey	CP	36.9 per 100,000	11.9 / 100,000	
	Hirota, 2014	Japan	2011	Large-scale nationwide survey	CP	52.4 per 100,000	14.0 / 100,000	-
	Tandon & Garg, 2004	India (Kerala)	2004	Survey	CP	4.2–114/200 per 100,000		-

Table 6.7: Results of the systematic search of prevalence, incidence and hospitalisation for chronic pancreatitis including current study for comparison

**CP - Chronic Pancreatitis. ACP – Alcoholic Chronic Pancreatitis. AP – Acute Pancreatitis*

6.12. Discussion

To the author's knowledge, this is the first systematic review of its kind of the prevalence, incidence and hospitalisation of chronic pancreatitis worldwide. There is a paucity of research, with only twenty-five studies meeting the criteria for full review. There was considerable heterogeneity in data collection methodologies throughout the studies. This is a limiting factor when comparing studies from different jurisdictions across different time periods, which used disparate study methodologies. Variations in disease estimates also result from difficulties in establishing accurate diagnosis, different diagnostic criteria and local lifestyle factors (40, 86). There is need for nationwide estimates of chronic pancreatitis disease incidence, prevalence and hospitalisations, which are absent from a number of countries worldwide. There is also need to investigate regional difference in demographic and disease distributions in order to accurately describe chronic pancreatitis epidemiology.

There is a lack of linkage between medical records in primary and secondary care is apparent in epidemiological studies worldwide and the same is true in Irelands. Shared patient information at different points of care requires significant infrastructural investment and linkage. Patient records must be integrated between, within and across healthcare services functioning across the entire sector in Ireland, and there is need for a unique patient identifier to enable comprehensive data collection in disease surveillance. Strengthening patient record integration and linkage can allow for the inclusion of all patients who utilise healthcare services, as currently there are cohorts of patients who remain invisible to epidemiological study.

6.12.1. Prevalence

Prevalence estimates in Europe and worldwide varies greatly, depending on the data collection methods used, and this has obvious implications for comparison and accurate measurement disease surveillance over time. To date, excluding the current study, the prevalence of chronic pancreatitis has only been estimated thirteen times. Despite the existence of a number of epidemiological studies, the true prevalence of chronic pancreatitis worldwide is not well described. This is due to the heterogeneous nature of the data, including single institution estimates, and a number of studies with small cohorts. Therefore, care must be taken when making associations or extrapolating findings to represent nationwide estimates. Nevertheless, the results of the included studies are interesting and certain patterns and similarities are evident.

Only one study in Europe has used registry data in the estimation of the prevalence of chronic pancreatitis (133). The authors reported an increase in prevalence during the study period (1980-2004) from 11.7 to 17.0 per 100,000, - slightly higher than a previous study in Denmark in 1981 (133, 376). The findings from the current study are comparable, albeit at the lower end of the estimate, and the populations of both nations are also similar (although Denmark is slightly higher than Ireland). Both the study from Denmark and the current study utilised methodologies accounting for counts of patients - or episodes of care. The Danish authors pointed to diagnostic improvements and increased duration of life as potential explanations for the higher prevalence. A primary objective of the Danish study was to describe chronic pancreatitis aetiologies, primarily any genetic associations which may exist in patients formally considered to have idiopathic aetiology by genetic testing. Interestingly, the authors found a high prevalence of genetic causes which partially or totally explained chronic pancreatitis in 55% of their idiopathic patient cohort.

In the US reports of chronic pancreatitis prevalence were higher, and have been estimated twice by Yadav and colleagues (82, 95). One study used Mayo Clinic Rochester's medical diagnosis index and a detailed chart review to identify incident cases of chronic pancreatitis and used this data to calculate age- and sex-adjusted incidence and prevalence rates. In this one US County, most individuals attend a single institution and a single primary care facility, which allows a more comprehensive population based estimate than studies which are based on hospital admissions alone. The authors are known to maintain large epidemiological and longitudinal databases of pancreatitis patients. Interestingly their rates of prevalence, which the authors considered to be in low, are in fact in line with primary care reports by Capurso (329) which will be discussed later. Again, the primary aetiology in the US was alcohol in 50% of cases. The second study by this group (95) used a single centre cohort of 1,409 alcoholic patients to estimate acute and chronic pancreatitis prevalence. In this instance, the authors found a low prevalence of pancreatitis but a moderate prevalence of acute pancreatitis in this high-risk population of heavy drinkers.

In Asia, a series of nationwide surveys have been conducted in both China and Japan reporting on prevalence, which appears to be increasing since 1994. In China, a survey was conducted in 22 central hospitals, and the data is inclusive of 2,008 patients, covering a 10 year period from 1994-2004. The authors requested detailed clinico-epidemiological data on all patients included in the survey including age, sex, year of onset, diagnosis, height, weight, daily grams of alcohol, years of alcohol abuse prior to onset, and pain. Results show a large increase in prevalence yearly from 3.08 to 13.5 per 100,000 and this study provides valuable epidemiological data due to the associated clinical data also collected. The collection of detailed epidemiological data allowed the authors to examine closely differences in aetiology, symptoms, diagnosis, and to examine the natural course of chronic pancreatitis in China. The authors reported year-on-year increase in prevalence of chronic pancreatitis in the whole of

China, and in each of the six healthcare regions. The fastest increase was reported in East China, which is thought to be the most modernised or westernised area. Similar to many western countries, the main aetiological factor in China was alcohol, and the authors point to social changes, industrialisation, increased discretionary income and more ease of access to alcohol as reasons for increased consumption. This survey differs from the Japanese survey series (136-138) in that the majority the patients with chronic pancreatitis in China were affected at middle age (139).

In Japan, seven consecutive studies have been carried out by RCIPD, providing nationwide estimates of prevalence from 1970 to 2011 (135-138). The first survey collected data from 2,017 patients with chronic pancreatitis between 1970 and 1977, the second survey collected data from 4,719 chronic pancreatitis patients between 1977-1984 (135). These first two surveys only collected data on patient numbers and contained no data about the at-risk population (135). The remainder of the nationwide surveys employed the same methodology, (i.e. two questionnaires sent to up to 4,000 Japanese hospital departments in each study). Stratified random sampling was used to choose departments of gastroenterology, internal medicine, digestive surgery and surgery where the patients were treated, and two different questionnaires were sent to each. The first questionnaire requested the number of chronic pancreatitis patients who were treated in the department in the year of study. Following the first survey, a second survey was sent to those departments who had reported seeing chronic pancreatitis patients in the first survey, and requested detailed epidemiological data on each individual patient, including; symptoms, diagnosis, aetiology, treatment, complications, and prognosis. Additional epidemiological data including socio-demographic factors, family history, financial subsidisation for treatment and medical care status were also surveyed. The prevalence increased substantially throughout these surveys from 28.4 in 1994 to 52.4 in 2011. This methodology of estimating numbers of patients treated in each department was based on the assumption that the departmental response was

independent of patient frequency, and this method has been shown to be valid (377) and replicated throughout the Japanese series. Again, similar to the Chinese and Western studies, alcohol was the predominant aetiology in this series which was associated with gradually increasing alcohol consumption in Japan (135). Other explanations for increased prevalence of chronic pancreatitis in Japan are increased disease awareness, improvement in referrals, and better and more widespread use of diagnostic modalities. These surveys provide valuable, in-depth epidemiological data on Japanese and Chinese chronic pancreatitis patients with the advantage of disease surveillance over a number of years, facilitating the comparison with earlier reports. This has also enabled the authors to draw conclusions, based on national or regional social changes, or changes in clinical practice during the study periods.

A number of studies used hospital based surveys to estimate disease prevalence. Levy *et al* (347) estimated prospectively national prevalence of chronic pancreatitis by surveying gastroenterologists in France and illustrated a higher prevalence than previously reported in France. However, as well as patients with confirmed chronic pancreatitis, those with recurrent attacks of acute pancreatitis were included, which may have accounted for increased numbers. Moreover, they calculated all consultations for chronic pancreatitis, without accounting for the possibility of multiple consultations with one patient. Both of these points may have falsely elevated the reported prevalence. In Spain (328), six pancreatic specialist units were surveyed and epidemiologic data were estimated according to the area served by each institution. They reported a prevalence which was more than four times the prevalence in the current study (Part A). Again, the data collected in this study was based on estimates of patient numbers, without the inclusion of individual patient counts or data, and therefore could be an overestimation of departmental caseload.

An Italian study (329), determined the prevalence of chronic pancreatitis in primary care, which is among the only study of its kind. Capurso *et al* (329) reported an

estimated prevalence of chronic pancreatitis in primary care of 30.2 per 100,000 for definite chronic pancreatitis patients, and 44.0 per 100,000 when definite and probable cases were combined. A slightly higher rate of chronic pancreatitis in non-alcoholic aetiology and among females was reported; half of the cohort was female with mild disease (329). This rate is higher than hospital-based chronic pancreatitis studies, and is among the only estimates of chronic pancreatitis in primary care worldwide. When patients are predominantly managed by GPs and endocrinologists in the outpatient / community setting, they are 'invisible' to hospital-based epidemiological studies. Quantifying the incidence and prevalence of chronic pancreatitis in the primary care setting is an important step towards describing fully the disease epidemiology. This Italian survey is similar to the French (327), Spanish (328), and Polish (326) studies, and though methodologically rigorous, and provide strong national observational estimates, the absence of exact counts of patients is somewhat restrictive. In the specialists or pancreatic unit surveys, patient numbers and incidence are calculated by the number of new cases, patient load prevalence, and population. There are sufficient grounds to question prevalence rates which have been derived from estimates of patient numbers, without the inclusion of individual patients. Difficulties arise in the comparison of these heterogeneous studies across different jurisdictions.

6.12.2. Incidence

The reported incidence of chronic pancreatitis also varies worldwide. In Japan, the RCIPD series has estimated that the incidence of chronic pancreatitis has increased over 17 year study period, from 5.4 to 14.0 per 100,000. Between the seven year period from 1992-1999, the incidence of chronic pancreatitis in Japan ranged from 5.4 to 5.8 per 100,000 (135). Although alcohol consumption was known to be increasing steadily at that time, as well as improved diagnostic accuracy (including the use of CT

or ERCP) these data indicate that the incidence remained relatively stable over a 7 year period (135). Comparing the present Japanese data with these earlier reports, the incidence (as well as prevalence) of chronic pancreatitis has continued to rise from 1994 to 2011.

Changes in incidence (and prevalence) are reportedly associated with continued increased alcohol consumption in Japan. Alcohol consumption reportedly increased continuously between 1965 and 2000 in Japan, and the rate in 2000 was 2.7 fold higher than 1965 (137). It is unclear if cigarette smoking has the same or any association with the disease increase. The authors of these studies also identified improvements in diagnostic sensitivity which has led to increased number of diagnoses; however, notwithstanding this assertion, it is clear that the incidence of chronic pancreatitis is increasing in Japan.

The reported incidence of chronic pancreatitis in Europe from a small number of studies is 1.8–7.9 per 100,000 of population (142, 333). In Germany (331), patient records of 74 chronic pancreatitis patients were used to estimate chronic pancreatitis incidence between 1988-1995. The authors of that study reported a similar incidence rate to a Danish study (334) which, included 126 patients from 1970-1979. Both of these studies had similar methodologies (chart review or retrospective study in small defined cohorts of patients) and both reported incidence rates of approximately 6 per 100,000. In France (347) in 2006 and the Czech Republic (333) in 1999, the incidence was approximately 7 per 100, 000, with the two study authors using comparable methods of hospital or specialist surveys. In the Netherlands, a gender difference was found from 1995–2005; the overall mean incidence was 1.8, which was 2.16 for males and 1.4 for females (142). In this small number of studies, the incidence rate has increased only marginally in Europe from 1962 to the latest report a decade ago in 2006. As discussed previously, the data collection methods were quite different between countries. However despite this, there was not a remarkable change over time.

In one of the earliest available reports published the clinical incidence of chronic pancreatitis between 1940 and 1969 was reported in one US county (144). The data contained 151 clinical cases and 170 incidental cases found on laparotomy or autopsy. The results showed an increased incidence of clinical cases of pancreatitis between the first and second decades (8.7–17.8). In another US study in the same state a number of years later, the incidence of chronic pancreatitis was reportedly lower, at 4.05 per 100,000. Reasons for the differences in reported incidence are due to the inclusion of both acute and chronic patients and incidental cases in the earlier study from the Mayo clinic, which may explain the higher incidence rates. The rate of 4 per 100,000 population is consistent with the median European estimate, - and with the surveys in the early nineties from the Japanese series. Again, and similar to Europe, there is a scarcity of nationwide estimates of chronic pancreatitis incidence (and prevalence) in the US.

In many of the European and North American countries where these studies have taken place, the smoking and alcohol consumption rates are stable, - or declining (318). Improvements in study methodology, knowledge, and diagnosis may reflect more accurate estimations in recent studies, rather than a large increase in absolute disease incidence. Considering the varied methodologies and lack of nationwide data and the dearth of well-designed, well-coordinated, national-level epidemiological studies, it is likely that the true incidence remains to date underestimated. One commonality among all of these studies is that there is a steadily higher incidence of chronic pancreatitis amongst the male sex; however there is a distinct lack of current-day estimates, or repeated large scale estimates which are comparable. Many of the available studies contain data from ten, twenty or thirty years ago. Again, there is a need for large-scale nationwide and more up-to-date epidemiological estimates.

6.12.3. Hospitalisation

A number of studies have examined chronic pancreatitis hospitalisation trends with variable results. In England (41), hospital episode statistics measured time trends in admission rates and reported a 100% increase in admissions for chronic pancreatitis during an 11-year study period. These findings are consistent with earlier reports from England, where discharges increased between 1980-1984 (335). This upward trend in hospitalisation rates was also reported in the Netherlands (146), where a 75% rise in chronic pancreatitis admissions between 1992 and 2004. A Finnish study reported a 26% increase in pancreatitis discharges over a 12 year period between 1970 and 1989, although coding did not allow the authors to separate acute and chronic pancreatitis (143).

A US study in one state reported that hospitalisation remained stable at 7.75 per 100,000 from 1996-2005 (336). Two conference proceedings reported different findings of reduced chronic pancreatitis-related hospitalisations. One (373) used an inpatient database and ICD-9 codes for CP (K577.1) (which at the time did not distinguish between acute-on-chronic and chronic pancreatitis) to determine the hospitalisation and cost of chronic pancreatitis. Hospitalisation rates decreased from 8.0 to 4.5 per 100,000 between 1997 and 2012. Furthermore, the mean length-of-stay decreased by 19.3%, (6.2 to 5.0 days) during this time. The second study (374) reported on hospital rates from 2002-2010, describes a decrease in primary diagnosis chronic pancreatitis hospitalisation, from 24,701 in 2002 to 19,809 in 2010 but reported that hospitalisation for secondary diagnosis of chronic pancreatitis more than doubled (from 65,987 to 143,691) during the study period. Where there was a secondary diagnosis of chronic pancreatitis, acute pancreatitis was the most common admitting diagnosis.

6.12.4. Methodological considerations

Results from this systematic review demonstrate that a wide range of methods have been used to collect epidemiological data on prevalence, incidence and hospitalisation of chronic pancreatitis worldwide. However, there remains a paucity of high-quality, nationwide studies on the prevalence and incidence of chronic pancreatitis which use exact counts of patients. The more accurate methods to estimate prevalence include national or regional databases, registries, hospital admission / discharge data, population surveys, and healthcare cost databases. Two studies utilised methodologies involving surveys of specialists, with one surveying gastroenterologists in France (327) and the other surveying pancreas units in Spain (328). Both of these studies reported notably high prevalence rates. It is plausible that surveying specialists regarding caseload may result in inflated estimated of patient counts. Also, by surveying specialist units, there is likely to be an element of spectrum bias, and therefore these surveys are unlikely to be representative of national data.

Chronic pancreatitis patients are followed-up regularly in primary care, and less often in hospitals, which may be especially true in middle and late stages of disease. Therefore studies on hospital data may be an inaccurate representation of the disease epidemiology. Only one study has investigated chronic pancreatitis prevalence in primary care. Capurso and colleagues (329) surveyed Italian primary care units and found a high prevalence of chronic pancreatitis. Although there is a possibility of disease misclassification by primary care physicians rather than pancreatologists, this estimate was in line with the reports from hospital-based surveys in Spain (134) and Japan (137, 138). Therefore, there is likely to be some degree of underestimation or overestimation in the various available studies. A method to overcome this inter-study and between-country variation is to conduct large-scale countrywide and population based studies, providing accurate epidemiological data.

6.12.5. Future directions

Advances in technologies including high resolution CT scanning means that chronic pancreatitis is now being diagnosed earlier, potentially accounting for the increases in prevalence and incidence reported in the Japanese studies. The contribution of environmental exposures, such as increased use of alcohol, may also be an important factor. Important genetic associations in population risk must be considered. The role of smoking, in the increase in incidence and prevalence had not been studied, and should be factored in to future research efforts.

The lack of uniformity in data collection methodology, data reporting and the diversity among countries worldwide, limits comparison of findings. Large, well-designed studies that are representative of the population in question are needed. There are variable prevalence, incidence and hospitalisation rates worldwide which are strongly affected by the data collection methods employed. In the future, more accurate epidemiological data may be identified by greater use of improved and accurate diagnostic modalities, such as high resolution CT and EUS. It is important that coordination of data recording on chronic pancreatitis patients' takes place at all points of care, by specialists, consultants, endocrinologists, nutrition services and GPs to provide a more complete knowledge of the disease. The prevention of a disease relies on studies to identify populations at risk, risk factors, environmental factors, health-status, and transmission of a disease within a population. These are aspects that must be overcome in order to produce large-scale epidemiological studies which can be compared between countries.

6.13. Study limitations and strengths

6.13.1. Limitations

There were a number of limitations identified in the current study. There was wide methodological diversity in the studies included in the search, limiting generalisability of findings. There is a possibility of case-selection bias, and spectrum bias in individual studies, which may inflate or deflate the true incidence prevalence of chronic pancreatitis. Furthermore, publication bias may have precluded the publication of low prevalence findings, which may overestimate the true prevalence. Some studies utilised small, single-institution cohorts of patients, and others were available only in abstract format. In some studies there was minimal reporting on methodology used to conduct the studies, which reduced the quality of the findings

6.13.2. Strengths

The study also had significant strengths. The searches were conducted systematically following a pre-defined methodology, and conducted with the intention of reproducibility of methods and findings. This study was supported by a medical librarian who also conducted the searches to improve accuracy and reproducibility of findings. Conference proceedings were included to reflect available research on the subject. The data reflects current and historical prevalence, incidence and hospitalisation of chronic pancreatitis, and data collated from thousands of patients worldwide, allowing for a good measure of prevalence using the available research. Gaps in current knowledge recommendations for future research have been identified, which have been drawn from analysis of the available studies.

6.14. General conclusion

To conclude chapter 6, this is the first study to estimate the prevalence of chronic pancreatitis in Ireland, and results were comparable to worldwide studies using similar a methodology. The findings confirm the value of the national administrative (HIPE) database. The data are further supported by the systematic search of published literature to enable quantification and comparison of findings, and situate Ireland among the worldwide estimates. Together these studies provide highly relevant information for the understanding of chronic pancreatitis in Ireland. These data are of use to clinicians, epidemiologists, pancreatologists, policy-makers, are will be vital in the allocation of sufficient resources for chronic pancreatitis management.

7. Chapter 7 – Small intestinal bacterial overgrowth in chronic pancreatitis

This chapter describes a prospective case-controlled, cohort study examining the prevalence of SIBO in alcohol and idiopathic non-surgical chronic pancreatitis patients with moderate and severe pancreatic exocrine insufficiency.

7.1. The intestinal microbiota

The intestinal microbiota consist of complex polymicrobial ecosystems, which have a number of important functions including; protection against pathogens, immune system protection, maintaining gut barrier integrity, and the production of various nutrients and vitamins (197). Disruption of microbial populations, which may occur for a number of reasons, may result in local and systemic consequences, including SIBO. In SIBO syndrome, the enteric bacteria of the proximal intestine resemble that of a healthy colon, where physiological microbiota are replaced by colonic pathogenic bacteria (211). The growth of these bacteria in the small intestine produces non-specific macro and microscopic mucosal inflammation which results in blunting of the villi and damage to the brush border (198). SIBO is usually associated with the failure of protective microbial defence mechanisms, anatomic anomalies, or motility disorders. This high bacterial concentration hinders normal small bowel nutrient absorption and patients develop malnutrition and gastrointestinal symptoms.

7.2. Introduction

7.2.1. Malabsorption and PEI in chronic pancreatitis

The pancreas has an essential role in digestion, as well as in maintaining glucose homeostasis. PEI occurs due to progressive destruction of pancreatic parenchyma. As described in Chapter 1, destruction of the acinar cells results in diminished production and secretion of digestive enzymes. Malnutrition and nutrient deficiency occur due to PEI, which effect nutrient digestion/absorption. This is further exasperated by poor dietary intake, (often) elevated alcohol intake, heavy smoking, chronic abdominal pain, and endocrine insufficiency. Malabsorption, pain, and other gastrointestinal symptoms are often difficult to manage in chronic pancreatitis patients (181). Clinically, patients

may experience weight loss, abdominal pain, bloating, vitamin deficiencies, sarcopenia, and complications of vitamin deficiency such as osteoporosis (112). PEI may occur even in the absence of symptoms such as pain (181), and results in weight loss (181), undernutrition (282), malabsorption, vitamin deficiency (378), and osteoporosis (112).

The gold standard treatment for PEI is PERT, which reduces fat malabsorption, and helps restore normal nutritional status (282). However, under-treatment is common (127) and patients may continue to have steatorrhoea and other adverse symptoms. Moreover, even with adequate PERT, patients may continue to experience adverse gastrointestinal symptoms (131), and other potential causes, such as giardiasis, SIBO (120, 379), and coeliac disease should be ruled-out (380).

7.2.2. Normal intestinal homeostasis

The bacterial concentration in the gastrointestinal tract increases in a caudal direction with the small intestine containing a minimum amount of gram positive aerobes. The stomach is almost sterile, and the upper aspect of the small bowel contains only a minute amount of bacteria. These bacteria are usually gram positive aerobes, and the presence of anaerobes is rare. Moving distally the bacteria begin to resemble those more commonly located in the colon (Figure 7.1).

There are a number of intrinsic mechanisms that control these enteric bacterial populations, including the number and type of bacteria in the healthy gastrointestinal tract. Gastric acid kills or inhibits ingested microorganisms before the small intestine is reached (211). Biliary and pancreatic secretions in the small intestine limit bacterial growth. The cleansing action of the antegrade peristalsis, especially migrating motor complex, reduces luminal growth potential and is responsible for sweeping bacteria into the colon (189). The intact ileocecal valve acts as a barrier to the backwards translocation of bacteria into the proximal small bowel (381). It is thought that the

normal endogenous homeostatic defence mechanisms prevent abundant microbial growth in the small intestine (129) (Figure 7.2)

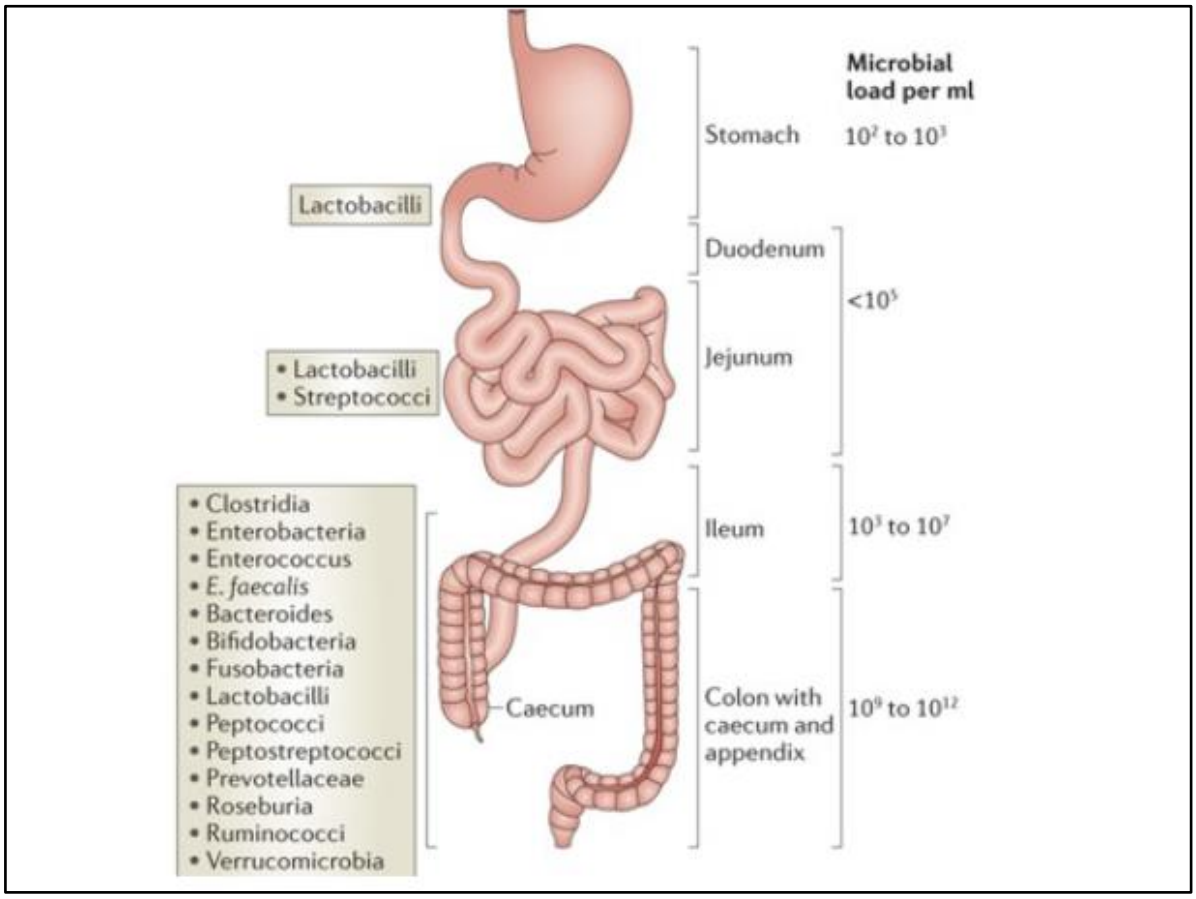

Figure 7.1: The gut microflora in healthy humans

Small numbers of bacteria reside in the stomach and small intestine which are typically gram positive aerobes, and anaerobes are rare. Anaerobes from the colon are not usually found in the proximal small intestine.

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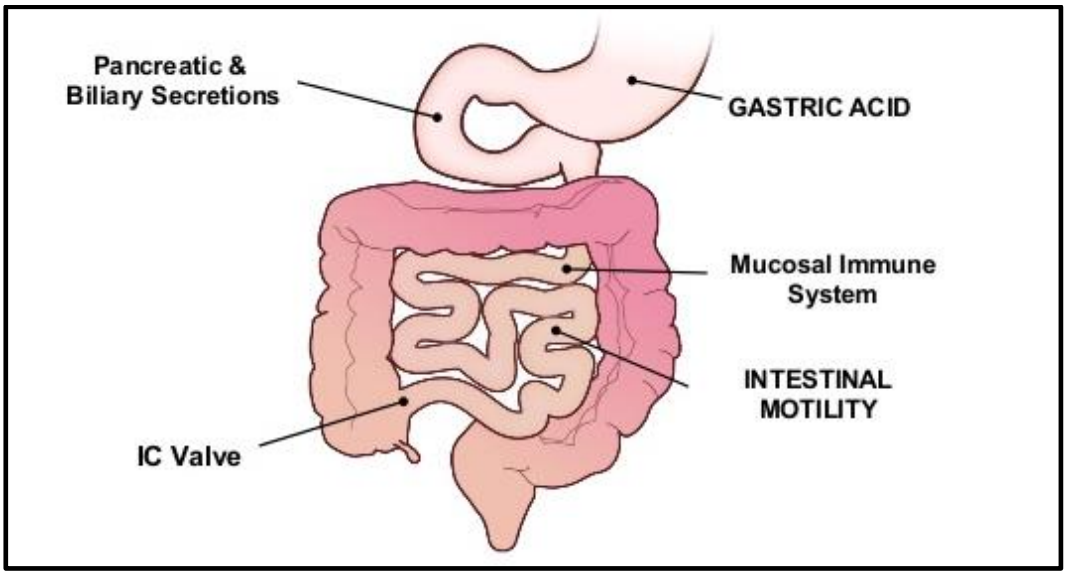

Figure 7.2: Protective mechanism against bacterial overgrowth

The mechanisms which may limit the growth of intestinal bacterial populations include anatomic and functional factors; gastric acidity, continence of ileocecal valve, bile and pancreatic secretions which have antibiotic properties, and mechanical factors such as intestinal peristaltic activity.

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7.2.3. SIBO

SIBO is defined as the presence of 10^5 or more colony forming units (CFU/ml) of bacteria, usually colonic enterobacteria, grown from jejunal aspirate culture (182, 189). Further to the absolute number of organisms, the type of microbial flora is known to plan an important role in the manifestations of signs and symptoms of overgrowth (384). For example, a predominance of bacteria that metabolise bile salts to unconjugated compounds may lead to fat malabsorption or bile acid diarrhoea (132). In contrast, carbohydrate-metabolising bacteria may produce symptoms of bloating without diarrhoea, as the metabolic products can be absorbed (132). Two types of SIBO are identified on the basis of pathophysiological mechanisms; 1) SIBO predominantly supported by gram positive bacteria from the upper respiratory tract,

secondary to a deficiency in gastric acid barrier, and 2) SIBO characterised by an increase in colonic bacteria, occurring in individuals with altered intestinal clearance or abnormal communication between large and small bowel (183, 185). SIBO is considered to be a malabsorption syndrome, and the clinical characteristics are largely varied in different subjects. Symptoms of SIBO are primarily chronic diarrhoea, weight loss, and signs associated with malabsorption of fat, carbohydrate, protein, vitamin B12, and other micronutrient, all of which significantly affect nutritional status and may affect quality of life (132, 198) (Table 7.2).

In several chronic diseases, SIBO may occur for a number of reasons (198) (Table 7.1).In patients with chronic pancreatitis the occurrence of SIBO is multifactorial and related to reduced intestinal motility, diminished pancreatic secretion, fat malabsorption, diabetic neuropathy, bile acid malabsorption, abdominal surgery, excess alcohol use and polypharmacy (182, 197, 198, 385-391). The use of gastric acid suppressants, which is common in chronic pancreatitis, predisposes to achlorhydria, and subsequently SIBO. Anatomic abnormalities and surgeries of the small bowel can lead to bacterial stasis and disrupt the protective mechanisms resulting in abundant SIBO by coliform bacteria (203). Gastrointestinal surgery is also thought to contribute to the development of SIBO by the creation of a stagnant afferent loop that often resulted in bacterial overgrowth (191). Small bowel strictures which may develop following small bowel surgery, (and also following radiation therapy or in patients with Crohn's disease) can also predispose to SIBO development (392). Ileocecal valve resection increases the risk of SIBO development due to bacterial backwash from the colon into the small intestine (203).

Alcohol, an important aetiological factor in chronic pancreatitis patients, can independently predispose to SIBO and this process is also thought to be multifactorial. Alcohol is thought to alter the small intestine defence mechanisms through structural

changes including; brush border enzyme depletion, epithelium loss, mucosal fibrosis, and through direct toxicity on the mucosal epithelium (387, 388, 393). Alcohol may affect the structure, motility and immune function of the small intestine, which precipitates bacterial overgrowth (394) and studies have demonstrated increased rates of bacterial overgrowth in alcoholics compared with abstainers (387, 388).

Steatorrhoea in chronic pancreatitis is difficult to treat, and whilst PERT is the mainstay of treatment, it is only thought to treat or resolve approximately 60-70% of the symptoms (395). In a number of patients, symptoms of PEI do not sufficiently improve, even with adequate doses of PERT, and investigations of other potential causes are required.

Mechanism	Specific Disorders
Failure of gastric acid barrier	• Atrophic gastritis (autoimmune, *Helicobacter pylori*) • Proton pump inhibitors • Hypochlorhydria associated with advanced age • Vagotomy • Subtotal or total gastrectomy • Gastric bypass
Failure of small bowel clearance	• Primary visceral neuropathies or myopathies • Connective tissue disease (scleroderma, polymyositis, mixed connective tissue disorder, lupus) • Radiation enteropathy • Paraneoplasmic syndrome • Amyloidosis • Muscular dystrophy • Medications • Idiopathic myenteric ganglionitis
Small bowel anatomic alteration	• Duodenal and jejunal diverticulosis • Fistulas, strictures • Blind loop syndrome (Roux-en-Y, gastric bypass, pancreatic transplant, others) • Resection of ileocecal valve
Local and systemic immune deficiency	• Combined variable immune deficiency • Hypogammaglobulinemia • T-cell deficiency
Systemic disease associations	• Chronic pancreatitis • Coeliac disease • Cirrhosis • Non-alcoholic steatohepatitis

Table 7.1: Physiologic mechanisms and various disorders associated with SIBO, including chronic pancreatitis

Adapted from (203)

- Weight loss
- Steatorrhea
- Gas – bloating
- Flatulence
- Diarrhoea
- Abdominal discomfort
- Vitamin / mineral deficiency
  - Fat soluble vitamin (A, D, E, K)
  - Vitamin B12
  - Iron
  - Thiamine
  - Nicotinamide
- Vitamin excess
  - Folate
- Hypoproteinaemia / hypoalbuminemia
- Decreased xylose absorption

Table 7.2: Clinical features and manifestations of SIBO

Adapted from (132, 198)

Considerations for SIBO testing in chronic pancreatitis	• Non-specific GI symptoms include; bloating, constipation, diarrhoea, abdominal cramps, distention, excessive flatulence, weight loss, malabsorption, maldigestion, nausea, vomiting • If concurrent PEI seek dietitian review to assess PERT adequate regime, dietary modification • Exclude giardiasis, coeliac disease, diabetic gastrointestinal disturbances, IBS, PEI, • Results of SIBO studies should be interpreted with caution, taking into account individual clinical history
Test methodology (183)	• Patients should remain antibiotic and laxative free for 4 weeks prior to breath testing • Strict minimum 12 hr pre-test fast • No non-fermentable carbohydrates, fibre in diet 24 hr prior to testing, and no lactulose in the final meal prior to testing • Refrain from alcohol and excessive exercise for 24 hr prior to study • Refrain from smoking for 12 hr prior to testing • Brush teeth and rinse mouth with chlorhexidine mouthwash prior to testing to reduce risk of substrate fermentation from oral bacteria flora • Take baseline breath sample prior to testing to ensure adequate fasting protocol. Patients with a high basal hydrogen level, should be re-educated regarding fasting protocol and re-tested following a 14 hour fast on another day • Test subjects ingest 50g glucose in 250ml water; breath samples retrieved every 15-20 min for 120 min • Patients must continue to fast during the study time • Test positivity is indicted with 10-12ppm increase in hydrogen excretion above baseline during testing. Two consecutive readings should confirm positivity
Negative result	• If no persistent rise in breath hydrogen excretion (>10ppm) above baseline during test time - negative test • Assess patient for the presence of other pathologies
Positive result	• Currently Rifaxamin 400mg TDS is recommended for SIBO eradication or antibiotic therapy as per local institution protocol • Assess patient post antibiotic therapy for symptom improvement
Retesting	• If no symptom improvement, consider retesting • Consider differential diagnoses

Table 7.3: Summary of Rome consensus guideline on H_2 breath testing for the diagnosis of small intestinal bacterial overgrowth (SIBO)

GI gastrointestinal, PEI pancreatic exocrine insufficiency, IBS irritable bowel syndrome, PPI proton pump inhibitor, PERT pancreatic enzyme replacement therapy, PPM parts per million, TDS three times a day

Rome Consensus Guideline (183)

7.2.4. Clinical features of SIBO

Although the clinical symptoms of SIBO have been reported in conjunction with several other conditions, little data is available on the clinical features of SIBO that occur specifically in patients with chronic pancreatitis. SIBO is generally considered to be a malabsorption condition, and the clinical features are thought to be similar regardless of the underlying predisposing factors for overgrowth. However, individual symptoms vary depending on the nature of the small bowel abnormality (191). Clinically, patients with SIBO may be asymptomatic, or may have symptoms which are similar to, and fit the diagnostic criteria of, irritable bowel syndrome (IBS) (200).

Common and non-specific symptoms of SIBO include nausea, abdominal distention / pain, and faecal urgency (130). Bloating and excessive flatulence in SIBO are thought to result from excessive bacterial fermentation in the small bowel. Disruption or inhibition of functional intestinal absorptive surface also plays a role in development of gas, bloating, and consequently, abdominal pain (198).

Diarrhoea is one of the primary symptoms of SIBO; however, the pathogenesis is unclear. It is thought that bowel habit is affected by the presence of the wrong type or nature of bacteria in the small bowel. Increased bacterial fermentation as a result of increased bacterial load in the small bowel also contributes to inflammation, which may lead to diarrhoea. Patients with irritable bowel syndrome and SIBO report the occurrence of diarrhoea more frequently than those with irritable bowel syndrome, but without SIBO (396). Carbohydrate malabsorption is common due to decreased absorption of peptide and amino acids, and weight loss in SIBO is thought to be related to fat and carbohydrate malabsorption (191, 200). Fat malabsorption (steatorrhoea) is known to occur in SIBO (191). Deconjugated bile salts, which reabsorb in the jejunum (as opposed to the ileum) lead to impaired micelle formation, and therefore fat malabsorption (132). Steatorrhoea further predisposes to the deficiency of fat-soluble vitamins (vitamins A, D, E, and K), and deficiency has been reported in patients with

SIBO (130), although the clinical symptoms are not thought to develop frequently. Vitamin B12 deficiency may also occur as a consequence of SIBO, and may result in macrocytic and megaloblastic anaemia. In severe or protracted cases of vitamin B12 deficiency in patients with SIBO, there may be neurologic damage, including posterolateral spinal cord demylelinisation, peripheral neuropathy and cerebral cognitive defects (191). In approximately one third of severe SIBO causing vitamin B12 deficiency, clinically apparent weight loss occurs secondary to steatorrhoea (211). The literature available regarding vitamin B12 deficiency in chronic pancreatitis patients with SIBO is contradictory, with studies describing both a low (44) and high (45) incidence of vitamin B12 deficiency. Deficiency of other B vitamins, including vitamin B1 (thiamine) and vitamin B3 (nicotinamide) have also been reported (130).

In contrast to reported vitamin deficiencies, bacterial synthesis and resultant absorption in SIBO syndrome may cause an elevated folate level in patients (198). This is thought to occur due to bacterial fermentation of substrates in the intestinal lumen which results in increased production of folate (397).

7.2.5. How to diagnose SIBO

Hydrogen and methane are by-products of small bowel bacterial fermentation of intraluminal substrates such as carbohydrates, which can be measured through lung air-expiration. The challenges of direct assessment of bacterial populations has led to the development of other less invasive techniques, including breath testing, which has become standard procedure in clinical practice. GHBT was introduced in 1976 for the assessment of SIBO (398). In an individual with SIBO, the proximally displaced bacteria (theoretically) should lead to glucose formation and result in an increase in hydrogen (399). In the classic description of the test, a single peak of hydrogen concentration after ingestion of glucose is indicative of SIBO (399). Breath-testing works on the assumption that the only source of hydrogen and methane production in

the body comes from bacterial metabolism of ingested substrates, usually carbohydrates such as glucose, lactulose, fructose, and xylose. Hydrogen and methane are produced by bacterial fermentation of ingested substrates, most frequently glucose and lactulose. Glucose has been deemed appropriate for SIBO detection (183), as under normal physiologic conditions it is absorbed in the small intestine (400). According to Rome Consensus (Table 7.2), any production of hydrogen during the 120 minute study time is indicative of carbohydrate metabolism by the presence of bacterial overgrowth in the proximal small bowel (183) (Figure 7.2)

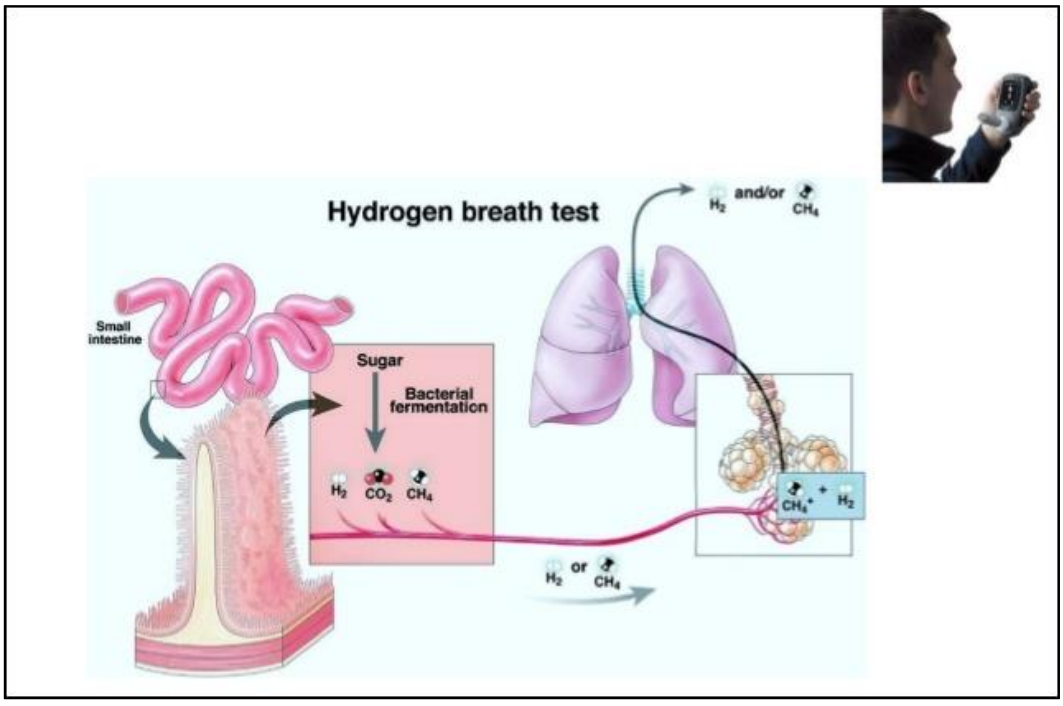

Figure 7.3: Hydrogen breath-testing of fermented substrate

This diagram illustrates the principles of the hydrogen breath test. Bacterial fermentation of an ingested substrate (glucose) is fermented by the presence of bacteria producing hydrogen (H_2) and methane (CH_4) which is absorbed into the bloodstream, carried to the lungs where it is released, exhaled and may be measured.

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7.2.6. SIBO prevalence

The prevalence of SIBO in the healthy general population is unknown, and due to unspecific symptoms (or in some case the presence of no symptoms) it is thought to be underdiagnosed. Between 30% and 85% of IBS patients are thought to have SIBO (402-405). SIBO has been reported in up to 90% of elderly patients with lactose malabsorption (406). SIBO has also been reported in liver cirrhosis (407), and coeliac disease (408), with an estimated SIBO prevalence in both diseases of up to 50% of cases.

In chronic pancreatitis patients, SIBO is reportedly present in up to 92% of cases (193) Studies on SIBO in chronic pancreatitis are generally limited by small sample size, heterogeneous patient groups, the use of unstandardized protocols, and differing methodologies.

7.2.7. Study rationale

SIBO is a known complication of chronic pancreatitis, however the prevalence varies widely (0-92%) (194), and the available studies differ in methodology and in patient type. To date, many of the studies have utilised lactulose as a substrate for breath-testing, which is contrary to the recommendations of the Rome Consensus (Table 7.2). The risk of SIBO in patients with a history of gastrointestinal surgery is known to be higher than in those with an intact gut, and few studies have investigated SIBO in a non-surgical population using the recommended substrate (192, 397). Therefore, there is a lack of knowledge of the true occurrence of SIBO in non-surgical patients with chronic pancreatitis, constituting a considerable research and clinical gap. This study aims to determine the prevalence of SIBO in a non-surgical patient chronic pancreatitis group, and to compare them to healthy non-pancreatic controls.

7.2.8. Study hypothesis

Non-surgical chronic pancreatitis patients with idiopathic or alcohol-related aetiology have a higher prevalence of SIBO when compared with matched, healthy controls.

7.2.9. Study objectives

- To investigate the prevalence of SIBO in non-surgical idiopathic and alcohol-induced chronic pancreatitis patients, and compared with age, gender and smoking-status matched healthy controls
- To determine the relationship between SIBO and clinical symptoms in chronic pancreatitis
- To examine medication use, PERT use and symptoms in chronic pancreatitis patients with SIBO
- To examine social factors in chronic pancreatitis patients with SIBO including smoking and alcohol use and employment status

7.3. Materials and methods

7.3.1. Study description

The study had a prospective case-controlled design, and patients with a diagnosis of idiopathic and alcohol-induced chronic pancreatitis were identified from a prospective pancreatic database maintained by the Professorial Surgical Unit (Trinity College Dublin) in Tallaght University Hospital. Patients were invited to participate in the study by letter, or recruited at weekly specialist pancreatic clinics in the Centre for Pancreatico-Bilary Diseases, Tallaght University Hospital.

A diagnosis of chronic pancreatitis was based on at least two of the following criteria: patient history (abdominal pain typical of pancreatitis), functional deficits (exocrine / endocrine impairment), and/or findings of radiologic / endoscopic studies (computed tomography / endoscopic ultrasonography), and the aetiology was determined by the pancreatic team. Idiopathic aetiology was diagnosed in the absence of other known clinical cause. Aetiology of alcohol-induced chronic pancreatitis was decided based on alcohol intake that exceeded recommended levels, and in the absence of other clinical causes.

7.3.2. Recruitment

7.3.2.1. Patient recruitment

Patients with alcohol-induced or idiopathic aetiology chronic pancreatitis were identified as eligible for the study and the study took place over a period of eight months in Tallaght University Hospital. Only patients with a documented faecal elastase-1 (FE-1) result confirming moderate (100-200ug/g) or severe (<100ug/g) PEI were included. Those without a documented FE-1 result were excluded. Patients were included if they had no history of surgery (gastric, pancreatic, intestinal), or a known diagnosis of a malabsorptive disease (Crohn's disease, ulcerative colitis, IBD, IBS, coeliac disease), or a diagnosis of cystic fibrosis, any malignancy, prognosis of less than 6month, or pregnancy. Only patients who were not acutely unwell at the time of the study were included. Patients had to be willing to attend one morning outpatient appointment. Participants had to remain antibiotic-free for four weeks prior to testing, and probiotics, prokinetics and laxatives were not permitted in the 14 days prior to testing. Each participant underwent subject suitability screening prior to inclusion (Appendix M), and were included if the strict study protocol could be adhered to.

Forty-two patients were excluded due to inability to adhere to the fasting protocol, inability to refrain from smoking during fasting or testing, or failure to attend appointments. Sixteen patients declined to be included in the study. Two patients with severe or 'brittle' diabetes and who were unable to fast were also excluded. This was determined on a case-by-case basis following discussion with the patient, and was related to safety issues with prolonged fasting, the risk of hypoglycaemia, and feasibility of safely driving to the research laboratory. Two patients had brittle diabetes and were deemed to be unsuitable for the study due to the requirement of a minimum 12 hour fast. In total, thirty-five unpaid Caucasian patients with chronic pancreatitis participated in the study.

7.3.3. Control recruitment

Control subjects were healthy men and women who were unpaid for their participation in the study. The study was advertised in the hospital, hospital intranet, in local businesses, community centres, local hospitals and taxi services (utilising a study poster, Appendix O) and through human resource departments. Control subjects were recruited from the same urban catchment area as patients and were closely matched for age, gender, and smoking status. Some of the controls were staff at the participating hospital, with the remainder recruited from businesses, factories and taxi services in the local area. Control subjects were unable to participate if a history of any surgery (gastric, pancreatic, and intestinal), malabsorptive disease, cystic fibrosis, pregnancy, malignancy, or if inability to adhere to the study protocol was reported.

7.3.4. Assessment

7.3.4.1. Glucose hydrogen breath testing (GHBT)

All patients and controls were required to adhere to a strict fasting and preparation protocol prior to testing. Patients were provided with written instructions regarding the minimum 12 hour fasting regime, advising the avoidance of slowly-released carbohydrates and fibre on the day prior to testing, and to avoid lactose or fructose in the last meal prior to fasting. Cigarette smoking was not permitted in the 12 hours while fasting, and participants were asked to avoid excessive alcohol and exercise for at least 24 hours prior to inclusion.

At the beginning of each appointment, subjects were instructed to brush their teeth and rinse their mouth with chlorhexidine-based mouthwash to eliminate the possibility of an early hydrogen peak from an oral bacterial reaction with the test substrate. SIBO was diagnosed through GHBT, using a portable hand-held breath analyser (LactoFAN H_2 Breath Test Analyser, Fischer Analysen Instrumente, Leipzig, Germany) which was calibrated and checked as per company standards and operating protocols. The study protocol was as follows; baseline fasting breath sample was obtained, the subjects were given 250ml of glucose substrate and remained fasting, and expired air breath samples were measured every 20 minutes for 120 minutes to measure H_2 excretion. An increase in breath-hydrogen levels of ≥12ppmH_2 from baseline (at least two readings) was diagnostic of SIBO. Patients with a high fasting basal breath hydrogen level, possibly suggestive of positivity, were re-educated regarding the fasting protocol, and retested following a 14 hour fast on another day. Clinical symptoms were evaluated pre-test and post antibiotic treatment (for those who tested positive) using a SIBO symptom checklist which was adapted for use (191, 200)

7.3.4.2. Exocrine function and PERT usage

To assess exocrine function, patients were required to have a documented FE-1 test result. This had been measured *via* stool sample using enzyme-linked immunosorbent assay during routine work-up at specialist pancreatic clinics. Patients' pre-existing recent FE-1 results (<2 years) was utilised to determine exocrine function without the need for additional laboratory testing. FE-1 was expressed as ųg/g of stool. Normal pancreatic function was >200ųg/g, moderate PEI was 100-200ųg/g and severe PEI was <100 ųg/g (282). The use of PERT was noted and the dosage of enzymes was recorded for each patient as a total dosage per day (units of PERT), and per Kg body weight.

7.3.5. Statistical analysis

Statistical analysis was conducted using SPSS Version 22 (SPSS, Chicago, IL, USA, 2015). Data were compared by means of Fisher's exact test and the Chi square test were used for categorical data. Continuous variables were analysed using a Student's *t* test for independent samples. A *P* value of <0.05 was considered statistically significant.

7.3.6. Ethical approval

This study had full ethical approval from the Tallaght Hospital / St James's Hospital Joint Research Ethics Committee (JREC) (Ref 2015-03) (Appendix B).

7.4. Results

7.4.1. Patient / control characteristics

Thirty five patients were evaluated for the presence of SIBO using a GHBT. Demographic and clinical characteristics of patients and controls are detailed in Table 7.1. Most patients (67%) were male, and the mean (standard deviation SD) age was 51.7 (11.1) years. Thirty-one healthy controls were recruited, of which 64% were male; and the mean (SD) age was 51.3 (11.4) years). By design, patients were matched for gender, age and smoking status. There was no statistical difference between patients and controls regarding gender (P=0.727), age (P=0.887) and smoking status (P=0.611).

The mean BMI of patients and controls was 26.0 kg/M^2 and 28.2 kg/M^2 respectively (P=0.402). More patients than controls had diabetes (P=0.009), used PPI (P=0.005), and used PERT (P=0.001). Of the 35 patients, 54.3% (n=19) had alcohol aetiology and 45.3% (n=16) had idiopathic chronic pancreatitis.

Patients had a higher intake of alcohol than controls, (mean 52.4 *vs* 18.7 units per week respectively, P=0.002). Chronic pancreatitis patients were more often taking benzodiazepines (P=0.016), antidepressants (P=0.008) and sleeping tablets (P=0.002) than control subjects.

7.4.2. Clinical symptoms

Chronic pancreatitis patients more often reported abdominal pain (P=0.001), weight loss (P=0.005), fatigue (P=0.010), body aches (P=0.001), abdominal distention (P=0.019) and diarrhoea (P=0.043). More patients than controls reported mild (51.4%) and severe (11.4%) pain (P=0.001). By study design, all patients had either mild (17.1%) or severe (82.9) PEI, while no controls had PEI. All symptoms reported were comparable between patients with and without SIBO. There was no difference in the

prevalence of symptoms in those without SIBO, with the exception of unintentional weight loss, which more commonly occurred in those with SIBO (P=0.047).

7.4.3. SIBO Prevalence

Five patients (14.3%) tested positive for SIBO, while no controls did (P=0.029). Four out of the five patients that tested positive for SIBO had alcohol aetiology. There was no difference in the smoking status of SIBO positive compared to SIBO negative patients (P=0.679). Chronic pancreatitis patients with concurrent diabetes (P=0.009) and who were taking PERT (P=0.016) and PPIs (P=0.022), were more often positive for SIBO. All patients that tested positive for SIBO had severe PEI, while no patients with mild PEI tested positive.

7.4.4. SIBO treatment

Chronic pancreatitis patients who tested positive were treated with Rifaxamin 400mg thrice daily for 10 days. All patients were followed-up by phone call on day 12 - 14 post antibiotic treatment where symptoms were reassessed and compared with patients' pre-test reports. All of the patients who tested positive reported a good clinical response and improvement in such symptoms as; flatulence, abdominal distention, abdominal pain, diarrhoea, constipation, weight loss, fatigue and body aches (Table 7.5). Following antibiotic therapy, and at the time of writing, there was no clinical need for re-testing.

	Patients (n=35)	Controls (n=31)	P- value
Age, mean (standard deviation SD)	51.69 (11.1)	51.29 (11.4)	0.887
Gender (M:F)	24:11	20:11	0.100
Smoking n (%)	18 (51.4)	14 (45.2)	0.611
Mean BMI (kg/m²)	26.0 (4.55)	28.2 (5.08)	0.341
CP aetiology (idiopathic : alcohol)	19:16	N/A	
Diabetes mellitus n (%)	16 (45.7)	3 (9)	0.009*
Pack year history, mean (SD)	26.2 (25.8)	16.9 (20.7)	0.151
Alcohol n (%)	27 (77)	28 (90)	0.152
Alcohol units (weekly), mean (SD)	52.2 (82.1)	18.7 (31.9)	0.002*
Surgery	0	0	-
Exocrine insufficiency n (%)			
Mild 100-200ug/g	6 (17.1)	0	N/A
Severe <100ug/g	29 (82.9)	0	N/A
Pain score n (%)			
0 = no pain	18 (51.4)	31 (100)	
1-3 = mild pain	13 (34.1)	0	0.001*
4-6 = moderate	4 (11.4)	0	
Opioid analgesics n (%)	10 (28.6)	0	0.001*
NSAIDS n (%)	17 (48.6)	7 (22.6)	0.028*
PPI use n (%)	17 (48.6)	5 (16.1)	0.005*
PERT n (%)	30 (86)	0	0.001*
Cholesterol medications n (%)	11 (31.4)	9 (29.0)	0.833
Blood pressure medications n (%)	11 (31.4)	7 (22.6)	0.421
Benzodiazepines n (%)	6 (17.1)	0	0.016*
Antidepressant medications n (%)	9 (25.7)	0	0.002*
Sleeping tablets n (%)	9 (25.7)	0	0.002*
Symptoms n (%)			
Flatulence n (%)	18 (51.4)	10 (32.3)	0.116
Abdominal distension n (%)	19 (54.2)	8 (25.8)	0.019*
Abdominal Pain n (%)	24 (68.6)	1 (3.2)	0.001*
Diarrhea n (%)	12 (34.3)	4 (12.9)	0.043*
Constipation n (%)	6 (17.1)	2 (6.5)	0.184
Weight loss n (%)	8 (22.8)	0	0.005*
Fatigue n (%)	16 (45.7)	5 (16.1)	0.010*
Body Aches n (%)	19 (54.3)	0	0.001*

Table 7.4: Characteristics of patients and controls

**Statistically significant P-value <0.05. SD standard deviation, BMI body mass index, CP chronic pancreatitis, NSAIDS non-steroidal anti-inflammatory drugs, Pain score (visual analogue scale 0-10), PPI proton pump inhibitor, PERT pancreatic enzyme replacement therapy.*

Results	Positive SIBO	Negative SIBO	P- value
Total positive and negative patients n (%)	5 (14.3)	30 (85.7)	0.029*
Age (mean, years)	53.0	51.4	0.638
Sex M:F	5:0	1.7:1	0.100
Smoking n (%)	3 (60)	15	0.668
BMI, mean (SD)	24.3	26.3	0.856
Aetiology n (%) Alcohol idiopathic	 4 (80) 1 (20)	 15 (50) 15 (50)	 0.023*
Diabetes mellitus n (%)	4 (80)	15 (50)	0.009*
PPI use n (%)	4 (80)	13 (43.3)	0.022*
PERT n (%)	5 (100)	25 (83.3)	0.016*
Symptoms n (%) *Flatulence n (%)* *Abdominal distension n (%)* *Abdominal pain n (%)* *Diarrhea n (%)* *Constipation n (%)* *Weight loss n (%)* *Fatigue n (%)* *Body aches n (%)*	 3 (60) 3 (60) 3 (60) 1 (20) 1 (20) 2 (40) 2 (40) 2 (40)	 15 (50) 16 (53.3) 21 (70) 11 (36.7) 5 (16.7) 6 (20) 14 (46.7) 17 (56.6)	 0.679 0.782 0.656 0.472 0.855 0.047* 0.650 0.489
Pain score n (%) *0 = no pain* *1-3 = mild pain* *4-6 = moderate pain* *7-10 = severe pain*	 4 (80) 1 (20) 0 0	 14 (46.7) 12 (40) 4 (13.3) 0	 0.358
Pancreatic exocrine insufficiency n (%) *Mild <200ug/g* *Severe <100-200ug/g*	 0 5 (14.3)	 0 24 (80)	 0.272
Opioids n (%)	0	10 (33)	0.127
Pain medications / NSAIDS n (%)	2 (40)	15 (50)	0.679
Cholesterol medications n (%)	2 (40)	9 (30)	0.656
Blood pressure medications n (%)	2 (40)	9 (30)	0.656
Benzodiazepines n (%)	1 (20)	5 (16.7)	0.855
Antidepressant medications n (%)	1 (20)	8 (26.6)	0.752
Sleeping medication n (%)	0	9 (30)	0.155

Table 7.5: Comparison of patient characteristics between those who tested positive and negative for SIBO

**Statistically significant P-value <0.05*

SD standard deviation, BMI body mass index, CP chronic pancreatitis, NSAIDS non-steroidal anti-inflammatory drugs, Pain score (visual analogue scale 0-10), PPI proton pump inhibitor, PERT pancreatic enzyme replacement therapy

7.4.5. Diabetes

Sixteen patients (46%) and 3 controls (10%) had diabetes (P=0.001) Chronic pancreatitis patients with concurrent diabetes were more likely to test positive for SIBO (P=0.009).

7.4.6. PERT and PPI use

Two thirds (68.6%) of patients reported having abdominal pain. Other reported symptoms were abdominal distention/bloating (54.2%) diarrhoea (34.3%), excessive flatulence (51.4%), body aches (54.3%), fatigue (45.7%) and weight loss (22.8%). More patients (48.6%) than controls (16.1%) were on PPI treatment (P=0.005). Those patients who tested positive for SIBO were also more frequently taking PPIs, than those who tested negative (P=0.002).

	SIBO 1		SIBO 2		SIBO 3		SIBO 4		SIBO 5	
	Pre-test	Post treatment	Pre-test	Post treatment	Pre-test	Post treatment	Pre-test	Post treatment	Pre-test	Post treatment
Flatulence	X	X	✓	X	✓	X	X	X	✓	X
Abdominal distension	X	X	✓	X	✓	X	✓	X	✓	X
Abdominal pain	✓	X	✓	X	✓	✓	X	X	✓	✓
Diarrhoea	X	X	X	X	✓	X	X	X	X	X
Constipation	X	X	✓	X	X	X	X	X	X	X
Weight loss	X	X	X	X	✓	✓	X	X	✓	X
Fatigue	X	X	X	X	✓	X	X	X	✓	X
Body aches	X	X	X	X	✓	X	X	X	✓	X

Table 7.6: Pre- and post-treatment presence of SIBO-related symptoms in patients (n=5) who tested positive for SIBO and were treated

Patients were assessed pre-test and post antibiotic treatment
Tick mark (✓) refers to 'symptom present', and X mark refers to 'symptom absent'
SIBO symptoms checklist adapted from (191, 200)

7.5. Discussion

7.5.1. The prevalence of SIBO

In a non-surgical group of chronic pancreatitis patients with either alcohol-related or idiopathic aetiology, there was a SIBO prevalence of 15%. While this is within the range of SIBO prevalence described by Capurso *et al* in their recent systematic review (194), it is in the lower range. This may be due to the recruitment of a non-surgical group.

The risk of developing SIBO is higher in patients who have undergone gastrointestinal surgery (409) due to the disruption of homeostatic mechanisms including; diminished gastric acid secretion, intestinal dysmotility, anatomic alterations and disturbances in gut immune function (132). Nine studies were included in the systematic review, and the reported prevalence was wide, ranging from 0% to 92%. However, only four studies investigated the occurrence of SIBO in patients that had not undergone surgery (192, 397, 410, 411). Of these, only two utilised the Rome Consensus guideline recommended substrate, glucose (192, 397), and found a SIBO prevalence of 0% and 21% respectively (192, 397). Conversely, the two studies that used lactulose substrate had notably higher prevalence of SIBO 69.9% (410) and 47.2% (411). Therefore, the current study (with a SIBO prevalence of 15%), was consistent with prior studies in non-surgical patients, using the recommended glucose substrate.

The prevalence of SIBO is also higher in patients with motility disorders, metabolic disorders, with organ dysfunction, in the elderly and in those who take recurrent medication (132). SIBO in chronic pancreatitis may result from fat malabsorption (181), diabetic neuropathy (386) alcohol-intake (387), and proton pump inhibitor use (412). Furthermore, for those experiencing PEI, the absence of anti-bacterial effect of proteolytic enzymes, the dysfunction in physiologic synchrony between inter-digestive

gastrointestinal motility, and reduced pancreatic secretion all favour the overgrowth of bacteria (131).

7.5.2. Diagnosing SIBO

7.5.2.1. The gold standard

Difficulties in establishing confident diagnoses of SIBO are related to the lack of gold standard investigations. Direct culture of small bowel aspirate is assumed to be the gold-standard. However, this method is impractical in clinical practice due to invasive cumbersome nature, the need for endotracheal intubation, poor reproducibility, unavailability of specific culture, bacteria cultivation-resistance, potential oropharyngeal contamination and high cost (197). The challenges of direct assessment of bacterial populations has led to the development of other less invasive techniques including breath testing, which relies on the collection and quantification of expired gas from bacterial metabolism of ingested substrates. Such methods are non-invasive, widely-available and inexpensive.

7.5.2.2. Lactulose hydrogen breath testing

Lactulose is a poorly absorbed disaccharide which reaches the cecum. A number of studies have evaluated the efficacy of lactulose in the evaluation of SIBO presence in IBS (207-210). Lactulose breath testing relies on a double peak criterion for positivity, the first peak within 90 minutes is thought to be bacteria in the small intestine, and the second peak is when substrate reaches the caecum. However, up to 50% of healthy individuals are known to have a rise in hydrogen within 90 minutes, often reflecting variations in transit time (205), and the use of this substrate is thought to result in fallaciously high positivity rates and is therefore not recommended in SIBO evaluation.

Many studies (207-210), have concluded that lactulose is insufficient for determining SIBO in IBS patients. Ghoshal (413) compared breath tests (GHBT/LHBT) with quantitative upper gut aspirate culture and found GHBT specificity of 100%. However, the sensitivity of this test was poor and therefore underestimation of SIBO is a possibility using this method. The authors reported that diagnostic performance of LHBT was poor. In the systematic review by Capurso *et al* (194), the pooled prevalence of SIBO in the six studies using GHBT was 22% *versus* 74% for the 3 studies using LHBT (194). Therefore, it is likely that the studies using LHBT have over-estimated the true prevalence of SIBO in chronic pancreatitis (Table 7.3).

Author (year)	Test	Patients	Aetiology	Surgery	Patient result	n, Control Characteristic	Control result	Statistical associations
Current study	GHBT	35	Alcohol / idiopathic	No	14.3%	n=31 Healthy, unresected	0%	Alcohol aetiology (P=0.023) Diabetes (P=0.009) PPI (P=0.022) PERT (P=0.016) Weight loss (P=0.047)
Therrien (2015)	LHBT	31	Alcohol /idiopathic/ obstructive/ cystic fibrosis/autoimmune/other	No	39%	n=40 Healthy	2.5%	Female gender (P=0.056)
Kim (2015)	LHBT	36	Alcohol/ Idiopathic/ autoimmune	No	47%	n=49 Healthy	27%	None
Kumar (2014)	GHBT	68	Alcohol / idiopathic	N/R	14.7%	n=74 Healthy	1.3%	None
Signoretti (2014)	GHBT	43	Alcohol / other	No	21%	n=43 Unspecified GI complaints	14%	Diarrhoea (P=0.01)
Grigor'eva (2010)	LHBT	102	N/R	No	69.6%	no controls	N/A	No
Mancilla (2008)	LHBT	14	Alcohol/ Idiopathic/ autoimmune	Yes	92%	n=14 Healthy	14%	No
Madsen (2003)	GBHT	11	Alcohol	No	0%	no controls	N/A	No
Trespi (1999)	GHBT	35	Alcohol	Yes	34%	n=61 Gastric resected	21%	No
Casellas (1998)	GHBT	15 : 15	Alcohol / idiopathic / hereditary	Yes	40%	Immunodeficient, surgical, mild PEI	6%	No
Lembcke (1985)	GHBT	15	Alcohol	No	40%	no controls	N/A	No

Table 7.7: Worldwide studies examining SIBO in chronic pancreatitis using either GHBT or LHBT testing

**Statistically significant P-value <0.05*

N/R not reported, N/A not applicable, GI gastrointestinal, LHBT lactulose hydrogen breath test, GHBT glucose hydrogen breath test, PEI pancreatic exocrine insufficiency, PPI proton pump inhibitor, PERT pancreatic enzyme replacement therapy

7.5.2.3. Glucose hydrogen breath-testing

GHBT has been found to have a sensitivity of 45% and specificity of 80% compared to jejunal aspirate culture (413). This is further corroborated by the findings of the Rome Consensus (an expert working group) who described a diagnostic accuracy of 72% for GHBT versus 55% for LHBT (183).The Rome Consensus Group (183) stated that the use of GHBT is recommended for the detection of SIBO in many gastrointestinal diseases including chronic pancreatitis. GHBT is non-invasive, safe and simple to conduct in clinical practice. The consensus group recommended a standardised protocol, (including fasting instructions), to aid standardisation (Table 7.4).

7.5.2.4. FE-1 testing

In the current study, patients who had FE-1 levels indicating moderate to severe PEI were included. There was no statistical difference between reported symptoms in the patients who tested positive and negative for SIBO. This may be an important indication in clinical practice, as patients positive and negative for SIBO may not differ in reported symptoms and clinical suspicion for SIBO is required. Testing of patients, especially those unresponsive to adequate-dose PERT, and whom have ongoing symptoms may be beneficial in clinical practice.

	Author (year)	Test	Patients	Aetiology	Surgery	Patient result	n, Control Characteristic	Control result	Statistical associations*
Non-surgical patients only	Current study	GHBT	35	Alcohol / idiopathic	No	14.7%	n=31 Healthy, unresected	0%	Alcohol aetiology (P=0.023) Diabetes (P=0.009) PPI (P=0.022) PERT (P=0.016) Weight loss (P=0.047)
Surgical history N/R	Kumar (2014)	GHBT	68	Alcohol / idiopathic	N/R	14.7%	n=74 Healthy	1.3%	None
Non-surgical patients only	Signoretti (2014)	GHBT	43	Alcohol / other	No	21%	n=43 Unspecified GI complaints	14%	Diarrhoea (P=0.01)
Non-surgical patients Only	Madsen (2003)	GBHT	11	Alcohol	No	0%	no controls	N/A	No
Non-surgical patients	Trespi (1999)	GHBT	35	Alcohol	Yes	34%	n=61 Gastric resected	21%	No
Non-surgical patients	Casellas (1998)	GHBT	15 : 15	Alcohol / idiopathic / hereditary	Yes	40%	Immunodeficient, surgical, mild PEI	6%	No
Surgical history N/R	Lembcke (1985)	GHBT	15	Alcohol	No	40%	no controls	N/A	No

Table 7.8: Worldwide studies examining SIBO in chronic pancreatitis using glucose hydrogen breath testing (GHBT)

**Statistically significant P-value <0.05*

N/R not reported, N/A not applicable, GI gastrointestinal, LHBT lactulose hydrogen breath test, PEI pancreatic exocrine insufficiency, PPI proton pump inhibitor, PERT pancreatic enzyme replacement therapy

7.5.3. The relationship between SIBO and various clinical and demographic factors in chronic pancreatitis

7.5.3.1. SIBO and age

In this study, SIBO was not associated with older age, which differs to the results reported in the literature. However, taking into consideration the mean age of patients and controls of 52 years, therefore, this cohort may have been too young to demonstrate this effect. Bacterial overgrowth has been assessed in between 14.5% and 33% of older adults using GHBT (414-416). The pathophysiology of SIBO in the aging was believed to be linked with age-associated reduction in gastrointestinal motility; however this has not been illustrated in a number of studies (417, 418). Instead SIBO in the elderly is thought to be due to pharmacological agents slowing gastrointestinal motility, the onset of comorbidities such as diabetes, decline in mobility, dietary changes leading to malnutrition and changes in gut immune function (132). Gastric hypochlorhydria has also been implicated as the driving force behind the development of SIBO in the elderly (418, 419).

7.5.3.2. SIBO and gender

Although the numbers were small, gender did not seem to be associated with SIBO prevalence in the current study. All of the patients who were SIBO-positive were male and there was no statistically significant difference in the group in terms of gender. Several studies have shown that female gender is a predictor of SIBO in IBS patients (389, 420), but this is thought to be due to higher prevalence of IBS diagnoses amongst females. Therrien and colleagues (421) noted a near significant association between SIBO in chronic pancreatitis patients and female gender (P=0.056).

7.5.3.3. SIBO and smoking

In the current study SIBO was not associated with smoking status. However, the current study was underpowered to assess an association as only three of the five SIBO positive patients were smokers. Of the available studies on SIBO in chronic pancreatitis, only one other study (421) identified the smoking status of patients and controls. The remaining studies (193, 397, 410, 422-424), did not report the smoking status of their subjects, and if there was a significant difference between patients and controls in terms of smoking habits, (which could potentially impact on results). One study (192), stated that patients refrained from smoking during testing; however, smoking should equally not be permitted on the day of testing due to the effect of smoking on hydrogen levels (183). During cigarette smoking, many gases are produced including methane, carbon monoxide and hydrogen; therefore smoking represents an important interference in breath testing (183). However, the precise role of environmental factors, such as smoking on SIBO development is largely unclear, although smoking is known to increase risk, the interplay requires further study. Cigarette smoking is known to be a primary environmental risk factor to the development of irritable bowel syndrome (425, 426). A profound alteration in intestinal microbiota has been described following smoking cessation in humans (427), indicating that smoking somehow modulates the gut microbiota composition. Studies on long-term effects of smoking on intestinal microbiota and SIBO risk are required.

7.5.3.4. SIBO and diabetes

Almost half of all patients (46%) were diabetic in the current study, which are consistent with international studies of chronic pancreatitis patients (192, 397, 411, 423, 424). In the present study a diagnosis of diabetes was more common in those who tested positive for SIBO, which is consistent with at least one other study (422). Reasons for an increased risk of SIBO in diabetics include gastrointestinal stagnation and lack of

antibacterial effect of proteolytic enzymes. It is thought that up to 75% of people with diabetes may experience gastrointestinal symptoms leading to poor quality of life and increased healthcare expenditure (428). Manifestations of diabetes affecting the GI tract include gastroparesis and enteropathy with symptoms occurring due to abnormal tract motility and diabetic autonomic neuropathy involving the tract (429). Furthermore, medications to treat diabetes, such as metformin, are believed to cause gastrointestinal disturbance is up to 30% of patients (430). As there is significant symptom overlap between SIBO, chronic pancreatitis, and gastrointestinal disturbances due to diabetes, diabetic patients should be tested for SIBO if they have relevant symptoms.

7.5.3.5. SIBO and alcohol

Alcohol is a known cause of chronic pancreatitis, and destroys acinar cells through direct toxicity, ultimately leading to fibrosis and gland failure (431). A number of studies have quantified the association between SIBO and excessive alcohol-drinking (387, 388, 432). However, even moderate drinking may be a strong risk factor for SIBO development (394).

The structure, motility and immune function of the small intestine is compromised with alcohol use, and previous studies have demonstrated that alcohol drinkers have higher rates of SIBO (387, 388). SIBO development in alcoholic populations is multifactorial and thought to be related to brush border enzyme depletion, epithelium loss, fibrosis and direct toxicity (388, 393). In alcoholic patients, the orocaecal transit time is increased in comparison with non-drinkers due to toxic intestinal muscle damage and diminished peristalsis secondary to alcohol (202).

7.5.3.6. SIBO and aetiology

This study suggested that there is a positive association between SIBO and alcohol-related chronic pancreatitis; however, the numbers were too small to provide robust evidence. Furthermore, this finding was dissimilar to that of other studies (396, 397, 422). While alcohol itself can predispose to SIBO, studies including only alcohol aetiology patients do not determine the impact of alcohol aetiology on the prevalence of SIBO. It is possible that the high prevalence of SIBO amongst chronic pancreatitis patients is due to pancreatitis itself and not due to alcohol ingestion as such. More studies are required to ascertain the impact of alcohol on SIBO in chronic pancreatitis.

7.5.3.7. SIBO and PEI

SIBO is associated with disorders of the protective antibacterial mechanisms. Cystic fibrosis and chronic pancreatitis patients are major risk factor patients groups for the development of SIBO (130). One risk factor which predisposes these patients is PEI with the absence of anti-bacterial effect of proteolytic enzymes (129, 130). Bacteriostatic pancreatic and biliary secretions are reduced or diminished during PEI, increasing the risk of bacterial overgrowth. There is evidence that antroduodenal motility is altered in chronic pancreatitis, and more so in patients with severe PEI (433). In this study there was no difference in SIBO prevalence when comparing moderate and severely exocrine impaired patients (however, as mentioned previously, the small numbers precluded such a comparison). Trespi *et al* (396) also failed to find a relationship between the severity of PEI and SIBO occurrence.

A number of studies have examined SIBO in chronic pancreatitis patients with concomitant PEI (192, 396, 397, 421-424). However, many did not specify the degree of PEI, and only two of these studies included patients with severe PEI. Furthermore, both included small cohorts of only 10 and 15 patients respectively (192, 423). One study reported that 43% of chronic pancreatitis patients with PEI continue to have fat

malabsorption despite treatment with apparently adequate PERT (434). It is plausible that patients with severe PEI may more often suffer from bacterial overgrowth, due to decreased enzyme action and continued fat malabsorption. SIBO should always be suspected in chronic pancreatitis patients where PERT treatment inadequately manages symptoms of PEI.

7.5.3.8. SIBO and PERT

The use of PERT was associated with the presence of SIBO in our cohort. Although SIBO should be suspected with intractable symptoms of PEI, there are no data to suggest that SIBO is more common in patients who are unresponsive to PERT (194). It is clear whether PERT itself is a direct cause of the development of SIBO per se, or if SIBO is caused by underlying PEI alone due to reduced pancreas enzyme activity. Because PERT therapy is usually not administered without PEI it is difficult to quantify the relationship between PERT and SIBO. The most probable explanation is it is related to the underlying PEI which PERT aims to treat.

7.5.3.9. SIBO and surgery

Surgery is known to predispose to SIBO risk as a result of anatomical alterations, changes in gastric acid post gastrectomy and surgical loss of the ileocecal valve. Structural abnormalities of the gastrointestinal tract, such as blind loop, provide ideal setting for intestinal overgrowth due to bacterial stasis, dysmotility, and ineffective clearance (132). The current study was designed to exclude those patients whom had previously undergone surgery as surgery is intrinsically a cause of SIBO.

7.5.3.10. SIBO and weight loss

Weight loss was the only clinical symptom which was noted to be associated with SIBO in chronic pancreatitis patients in the current study. Weight loss among chronic pancreatitis patients appears to be common and has been reported in 49% of cases (127). Patients with Crohn's disease and SIBO reportedly have a lower body weight than those without SIBO (392). In Crohn's disease, SIBO is a clinically relevant complication of underlying disease, which may mimic acute flare-ups. This could potentially be similar in chronic pancreatitis patients due to the ongoing inflammatory nature of the disease. Unintentional weight loss in symptomatic chronic pancreatitis patients could be an important marker for investigation and targeted work-up for other pathologies, such as SIBO. Additionally, ongoing malabsorption of macronutrients coupled with gastrointestinal symptoms may result in reduced dietary intake which may further cause weight loss. Chronic pancreatitis and SIBO both have similar clinical symptoms, which could account for the absence of significant difference between the malabsorptive and digestive symptoms in those with positive and negative patients.

7.5.3.11. SIBO and PPI use

In the present study SIBO was positivity associated with PPI use, a finding which was similar to other studies of gastrointestinal disorders. PPI use in this cohort was common, with almost half of patients (48%) taking PPIs. Only 16% of controls were taking PPIs. PPIs (or similar acid suppression medication) are commonly prescribed in chronic pancreatitis due to a reduction in the secretion of bicarbonate-rich fluid by the pancreas, which results in an acidic stomach and small bowel. The addition of acid-suppression medication increases the pH of the small bowel, and prevents the denaturing of both endogenous and exogenous pancreatic enzymes, thereby improving symptoms of PEI. A recent large systematic review of studies including 3,134 adult patients (412) found that PPI use was strongly associated with SIBO risk, but only

when the diagnosis was made through duodenal or jejunal aspirate culture. Another study postulated that since IBS patients are prescribed PPI therapy more often than controls, they are more likely to develop SIBO (435). Several studies have demonstrated that hypochlorhydria observed by the use of PPI therapy, is a risk factor for SIBO (186, 436, 437). Lewis *et al* (186) found that omeprazole was associated with SIBO and rapid intestinal transit time. Thorens *et al* (436) demonstrated that gastric and duodenal bacterial overgrowth was significantly higher in patients treated with omeprazole compared to cimetidine, which is histamine (H2) blocker.

7.5.3.12. SIBO and other medications

The sustained use of narcotic drugs has been implicated as a risk factor to the development of SIBO in a number of diseases. There was no relationship between the use of narcotics and the prevalence of SIBO in the current study, a similar finding to other studies on chronic pancreatitis patients. Again, the study is likely to be underpowered to detect this association. There were considerably more patients than controls taking various medications such as cholesterol, antihypertensive, antidepressants, benzodiazepines, night sedation and pain relief. This is an indication of the co-morbidities and complications associated with chronic pancreatitis. Despite a lack of association in this study, opiate analgesics are known to slow intestinal motility (438) providing conditions for bacterial overgrowth.

7.5.4. SIBO treatment

In the current study, though from a low base, the treatment of SIBO with antibiotics in chronic pancreatitis patients has demonstrated symptom improvement, which is similar to a number of other studies (422, 423). However, there have been few randomised placebo-controlled studies in other gastrointestinal diseases, and the available studies have included small cohorts of patients (439, 440). A recent systematic review and

meta-analysis of Rifaximin for the treatment of SIBO involving 1,331 patients concluded that it is safe and effective for the eradication of symptoms; however, well-designed studies are required to establish optimal antibiotic regimens.

7.5.5. SIBO retesting

Whilst a follow-up was not among the aims of the study, the subject's responses to treatment were documented. Importantly, symptom improvement was reported in all patients following antibiotic therapy for the eradication of SIBO. Patients were not retested due to self-reported symptom relief post antibiotic therapy. Patients are closely monitored in specialist clinics for future symptom recurrence. According to Rome consensus, repeat breath testing is not indicated once there is symptomatic response and the mainstay of treatment is antibiotic therapy to eradicate symptoms (183). However, evaluation of symptoms pre-test and post-treatment is helpful to appraise the effect of antibiotic treatment on symptoms, or the need for further intervention. None of the patients required re-testing at the time of writing. There are no studies available on the recurrence of SIBO following treatment in chronic pancreatitis patients. Additional research is required to investigate SIBO, antibiotic treatment, and symptom improvement in patients with chronic pancreatitis

7.5.6. Clinical Implications

Clinicians who suspect SIBO in patients with chronic pancreatitis should arrange breath-testing early to exclude the condition, or to allow targeted antibiotic treatment. Early detection and subsequent treatment of SIBO will serve to reduce the risk of syndrome-associated defects. GHBT is widely available, simple, and inexpensive, and studies have demonstrated its utility in SIBO diagnosis. However, care should be taken when interpreting the results, and in combination with clinical findings (Table 7.3). SIBO

may require several courses of antibiotics to eradicate bacterial overgrowth, and retesting of patients may be necessary. The ability to easily evaluate SIBO presence is relevant in clinical practice due to the resource impact and potential consequences of prophylactic antibiotic treatment for all symptomatic patients.

7.6. Limitations and strengths

This study had a number of limitations. Breath testing is limited due to the inability to differentiate between bacterial types colonising the small bowel, thus limiting precise antibiotic selection for bacterial treatment. The glucose breath test identified only hydrogen-producing bacteria; however, according to Rome consensus guidelines (183), the measurement of breath methane is currently not recommended to improve diagnostic accuracy of the hydrogen breath test. GHBT is limited in that is evaluates only the presence of proximal small bowel bacterial overgrowth, as glucose is fully absorbed prior to entry into the caecum. The small number of patients who tested positive can be seen as a limitation to the associations reported.

Notwithstanding these limitations, the study has significant strengths. Data were collected consecutively, prospectively, and in a strict and standardised manner. The study protocol and fasting preparations were based on best available research evidence and consensus guideline. Patients and controls were tightly matched in terms of age, gender, smoking status, and were also similar in terms of alcohol intake.

7.7. Conclusion

SIBO was present in almost 15% of this well-defined cohort of idiopathic and alcohol aetiology non-surgical chronic pancreatitis patients with mild and severe pancreatic exocrine insufficiency. Data from this study are consistent with findings from other studies worldwide employing a similar methodology of GHBT, excluding surgical patients, and including healthy controls. Many chronic pancreatitis patients continue to have ongoing abdominal, intestinal and malabsorbtive symptoms despite apparently adequate PERT treatment. SIBO symptoms may overlap with those of PEI in chronic pancreatitis, and should be considered in nonsurgical patients where PERT insufficiently treats gastrointestinal symptoms, and particularly in the presence of concurrent diabetes. Symptom improvement post antibiotic treatment was reported in all patients which is clinically significant. SIBO symptoms are often difficult to differentiate between underlying diseases, therefore targeted work-up is recommended in chronic pancreatitis patients with corresponding clinical signs and predisposing factors. Breath testing is an efficient, non-invasive and inexpensive method to assess the presence of proximal small bowel bacterial overgrowth of chronic pancreatitis patients in clinical practice.

8. Chapter 8 – Genetic analysis of major pancreatic gene mutations in chronic pancreatitis patients

As discussed in previous chapters, the pathogenesis of chronic pancreatitis is a complex, multifactorial process with factors including smoking, excessive alcohol use, hypertriglyceridemia, as well as environmental factors increasing disease risk. However, there is also sufficient evidence to suggest that individual genetic susceptibility may contribute significantly to disease development. The important contribution of common pancreatic gene mutations to disease development has been documented in studies in a variety of cohorts.

In Ireland more than 1 in 20 people are thought to be carriers of a recessive cystic fibrosis gene mutation, contributing to a relatively high prevalence of cystic fibrosis in this country. How this commonly-occurring cystic fibrosis gene mutation affects the development or prevalence of chronic pancreatitis has not been investigated.

This chapter describes a prospective control-cohort study that investigated major pancreatic gene mutations, amongst a well-defined group of idiopathic and alcohol-induced chronic pancreatitis patients.

8.1. General introduction

Chronic pancreatitis is a challenging and complex genetic disease. Therefore genetic analysis should arguably be central to the management of this pancreatic disorder. Previously, it was believed that alcohol was the most important factor driving chronic pancreatitis development. Until more sensitive technologies to identify mild chronic pancreatitis were developed, most clinico-epidemiological studies only identified the most severe cases, and reported that chronic pancreatitis was essentially a disease of alcoholic males (66). However, although the role of alcohol appears to be a significant aetiological factor in predisposed patients, there are high numbers of patients in whom the cause remains unclear, despite sophisticated imaging and biochemical investigations. Genetic studies of chronic pancreatitis over the last two decades have made great progress in defining disease pathogenesis and the underlying genetic susceptibility, which increases risk of pancreatic damage. Chronic pancreatitis is now understood as a complex genetic disorder involving various gene-environment interactions, gene-gene (epistatic) interactions, or more complex interactions, that together result in significantly increased or decreased risk of developing organ injury or dysfunction or modifying the nature of severity or disease process (101).

Patients with chronic pancreatitis are subject to a complex genetic disorder (219). The diagnosis of chronic pancreatitis is difficult, especially in early disease, and the diagnosis is often reached years after initial pancreatitis attack when structural or functional effects become evident (115, 441). Knowledge and understanding individual genetic susceptibility and aetiological pathway can allow critical insights into targeting the underlying problem (66). Whilst a few studies have examined the association of major pancreatic gene mutations in chronic pancreatitis patients, no cohorts have been examined in Ireland, and only a minority from the UK. The presence of genetic mutations provides clinicians and patients with more understanding of the cause of disease. This is particularly important in patients who have alcohol-related disease, as

literature evidences that many patients have sub-threshold excessive alcohol consumption, required to initiate disease (94, 331, 352). Currently genetic testing is not part of standard diagnostic work-up, besides the examination of *PRSS1* mutations in hereditary pancreatitis patients. The management of disease and prevention of recurrence require knowledge of the underlying aetiology and patient specific risk. Genetic testing can provide clinicians and patients with knowledge, and research can decipher the burden of genetic associations amongst chronic pancreatitis patients (101, 219). By clarifying the nature of pancreatitis susceptibility genes in chronic pancreatitis, protocols for assessments and management of patients may be formulated to optimise the diagnosis of patients, allowing targeted aetiology-based patient care.

8.1.1. Genetics of chronic pancreatitis

In recent years there has been increasing recognition of the causative role of genetic variants in the development of chronic pancreatitis, both idiopathic and alcohol-associated. As discussed in Chapter 3, the principal susceptibility genes currently known, are *PRSS1, SPINK1, CTRC, CASR* (which target the acinar cells through trypsin-dependent pathway), or *CFTR* (which target the duct cells). Chronic pancreatitis patients are predominantly divisible into two groups based on aetiology: those who develop chronic pancreatitis secondary to environmental exposures (including excessive alcohol consumption and heavy smoking), and those who develop the disease spontaneously for unknown causes, deemed idiopathic. The latter group account for approximately 19-30% of cases (85, 114, 442). Much of the variability in susceptibility to recurrent acute pancreatitis and chronic pancreatitis has been shown to be related to genetic differences between patients (219). Research in the past several years has suggested that the molecular underpinnings of chronic pancreatitis are driven by genetic mutations of the trypsin enzyme cascade. Gain-of-function mutations in *PRSS1* gene, as well as loss-of-function variants in *SPINK1* and *CTRC*

genes increase the risk for pancreatitis (51, 102, 106, 443). In fact, about a half of non-alcohol-associated cases of chronic pancreatitis, a genetic background has been identified, with mutations in *PRSS1*, *SPINK1* and or *CTRC* through mechanisms of intra-pancreatic activation of trypsin (51, 102, 106, 444).

Aside from the components of the trypsin cascade, another important gene has been implicated in disease pathogenesis, namely *CFTR*. Two severe loss-of-function mutations in *CFTR* cause cystic fibrosis, a disease which is characterised by lung disease, pancreatitis, and PEI. However, *CFTR* mutations, sometimes in combination with other mutations (*SPINK1*), have now been demonstrated in several chronic pancreatitis cohorts (104, 239, 445). This provides evidence that carrier-status of cystic fibrosis mutations can confer an increased pancreatitis risk. Mechanisms of *CFTR*-related genetic risk are associated with dysfunction in bicarbonate secretion into the duct lumen. *CFTR* is one of the only genes, outside of those involved in the trypsin cascade, consistently shown to be associated with chronic pancreatitis.

8.1.2. Aetiology and genetic testing

Despite the growing recognition that genetic variants have a role in the development of pancreatitis, there is still uncertainty regarding which patients with idiopathic pancreatitis should undergo genetic evaluation (446). The nationwide study on patient discharges for chronic pancreatitis in Ireland (Chapter 4) found that the majority of hospital discharges were associated with non-alcohol aetiology (447). This therefore suggests that other factors, including genetic predisposition, may contribute to disease pathogenesis. It is also possible that other genes remain to be discovered, given that only minorities of cases, perhaps up to 50%, have a known associated mutation to date. Further evaluations of factors associated with pathogenic variants in patients with idiopathic and alcohol-induced chronic pancreatitis are required. This in turn will enable

a more thorough aetiological diagnosis, and will ameliorate the treatment pathway for chronic pancreatitis patients.

Genetic and environmental assessment may help in the early identification of patients who are likely to develop *severe* chronic pancreatitis, thereby allowing targeted attention to reduce confounding risks and slow or limit disease in the future (61). Complex multifactorial diseases such as chronic pancreatitis require a comprehensive analysis of a range of potential susceptibility variants to support modelling of the effects of genes and environment. Therefore beyond genetic mutations, the context within which mutations exist must be considered, which in patients with chronic pancreatitis includes the inflammatory response, clinical, and exogenous factors (448).

As described, functional analysis of several identified gene mutations has shown that they result in either gain of trypsin function (*PRSS1*), loss or decreased protein function (*SPINK1*) and/or altered ductal secretion (*CFTR* mutations). Whilst many major pancreatic gene mutations have been discovered in chronic pancreatitis patients, the present study will focus on only a select group of variants which have most commonly been demonstrated in various studies.

8.1.3. Genetic associations in chronic pancreatitis

The genetics of chronic pancreatitis are complex, and the pathophysiological mechanisms first require clarification in order to understand the concepts. Chronic pancreatitis is a complex syndrome of signs and symptoms, rather than an isolated disease, and multiple causative pathways converge into similar phenotypic features. The process most often begins with acute and recurrent acute pancreatitis (219). The onset, severity, complications, and clinical course of chronic pancreatitis are unpredictable, and tend to differ significantly between patients of similar aetiology (219). Environmental and genetic risk factors significantly alter the probability of an

event or outcome, and therefore are useful to clinicians in predicting the severity, complications clinical course and individual patient response to treatment (219).

8.1.3.1. PRSS1 gain-of-function mutations (R122H, A16V, N29I) in chronic pancreatitis

The causative role of trypsinogen in pancreatitis is supported by the identification of mutations in the *PRSS1* gene of patients with hereditary pancreatitis (51, 449-451). The trypsin-dependent pathological pathway of chronic pancreatitis model (outlined in Chapters 1 and 3), shows that elevated levels of active trypsin in the pancreas elicits disease onset and drives progression, and that the combined effects of mutations in various susceptibility genes determines intra-pancreatic trypsin activity (234). Important gain-of-function mutations (namely R122H, N29I, and A16V), have been associated with hereditary pancreatitis. Mutations in *PRSS1* that increase autoactivation of trypsinogen are strong risk factors for chronic pancreatitis, and have typically been associated with hereditary pancreatitis (234). The functionality of the *PRSS1* gene mutations are described in Table 8.1. Protective mechanisms in the pancreas that curtail trypsinogen activation (and therefore reduce trypsin activity) involve either trypsin inhibition or degradation. Most *PRSS1* variants increase intrapancreatic trypsin activity by stimulating trypsinogen activation and/or by inhibiting *CTRC*-dependent trypsin degradation (452) (Figure 8.1). However some *PRSS1* variants cause trypsinogen misfolding, which results in the intracellular retention and degradation with consequent endoplasmic reticulum stress (452).

The R122H was the first identified *PRSS1* mutation, and remains the most commonly-found mutation in hereditary chronic pancreatitis (51), and has been detected in half of all hereditary chronic pancreatitis patients (453). Two distinct nucleotide substitutions are known to lead to R122H mutations (c.365G>A, and c.365-366GC>AT), the latter

being associated with idiopathic chronic pancreatitis (453-455). A large European study to determine the phenotype-genotype correlations of hereditary pancreatitis found that R122H carriers presented at a younger age, but took longer to reach disease endpoints, and had much higher levels of exocrine and endocrine failure when compared to other forms of pancreatitis. (450). This study also demonstrated that those with N29I mutation of no mutation, had lower hospital admission rates than those who wit mutated R122H (450).

N29I is the second most frequently-detected *PRSS1* gene mutation (220) and like R112H mutation, is typically found in patients with hereditary forms of pancreatitis. However in the clinical setting, obtainable family history may be limited, and patients may present with what appears to be sporadic disease (452).

The A16V mutation is the third most common *PRSS1* gene mutation, and has been detected not only in hereditary chronic pancreatitis, but also in idiopathic chronic pancreatitis (223, 456). The presence of *PRSS1* mutations is considered to be extremely rare in the general population in the absence of disease (222, 457, 458).

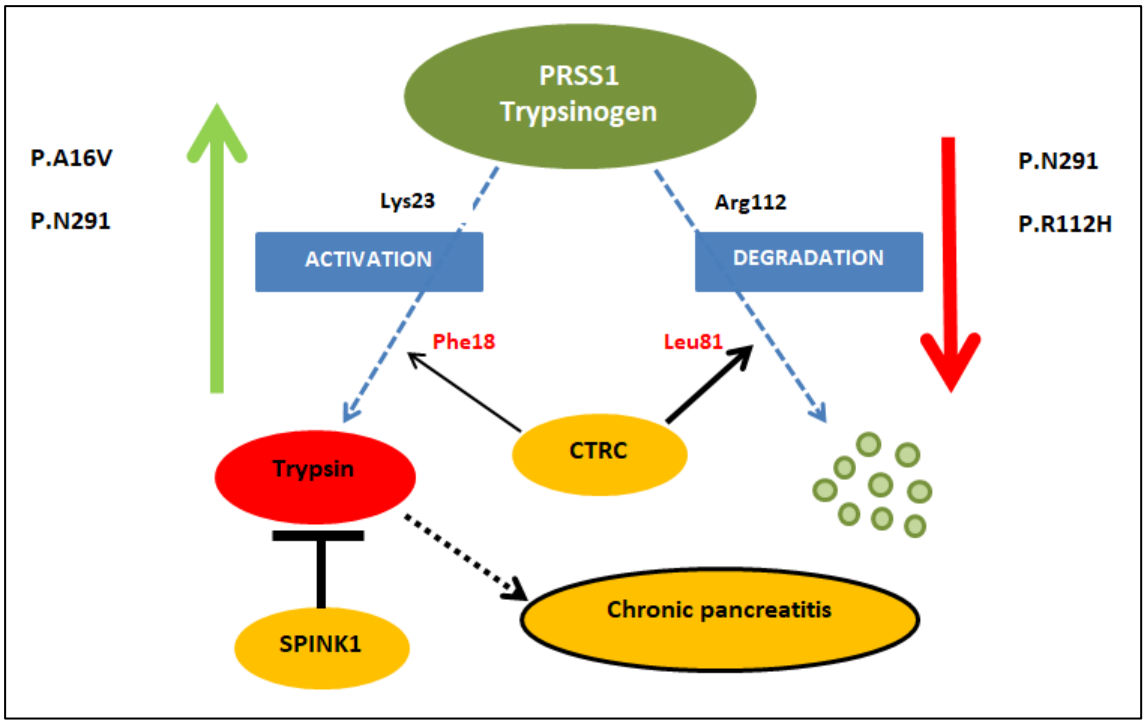

Figure 8.1: The trypsin-dependent pathological pathway in chronic pancreatitis

Activation of PRSS1 trypsinogen to active trypsin in the pancreas is responsible for disease onset and progression. Protective mechanisms that control trypsin activation include trypsin inhibition by SPINK1 and trypsin degradation by CTRC and trypsin. CTRC cleaves (LEU81-Glu82) and trypsin cleaves (Arg112-Val123) peptide bonds, and the combination of this cleavage results in irreversible trypsinogen degradation. CTRC also stimulates autoactivation of PRSS1 in the activation peptide (by cleaving Phe18 peptide bond and the shortened activation peptide is more susceptible to trypsin-mediated activation (at Lys23-Ile24 peptide bond). Hereditary pancreatitis associated PRSS1 mutations increase trypsinogen autoactivation by inhibition of CTRC-dependent trypsinogen degradation (red arrow), and by increasing CTRC dependent stimulation of autoactivation (green arrow) (mutations highlighted in black). Loss-of-function mutations in SPINK1 reduce inhibitor expression compromising trypsin inhibition. Loss-of-function mutations in CTRC reduce secretion, block zymogen activation, diminish catalytic activity or promote degradation by trypsin and therefore impair trypsinogen degradation.

Figure and description modified and re-used from (234, 452)

PRSS1 mutation	Functionality
R122H	The arginine (R) at position 112 is the primary autolysis site of trypsin. Because of the substitution of R by histidine (H) in this mutation, the autolysis site gets lost and trypsin becomes resistant against inactivity mechanism (51). Further active and inactive trypsin become more stabilised and shows more auto-activation (459).
N29I	The exact mechanism of N29I is unclear. Functional analysis showed an enhanced auto-activation, but no inhibition of autolysis (459). The N29I substitution leads to conformational changes influencing the R112 lysis site and making it insensitive for the cleavage of peptide bonds by trypsin (trypsinolysis) (51)
A16V	The A16 position is the cleavage site of signal peptide and activation peptide. Loss of this cleavage site is thought to result in either a.) a disturbed secretion of pre-proteins and a possible intracellular activation or formation of trypsin instead of an inactive precursor, or b.) a conformational change of the activation peptide with increased autoactivation (223, 460). The mutation A16V is associated with a x4 times faster stimulation of trypsin by the *CTRC* protein, causing accelerated trypsinogen activation (461).

Table 8.1: Functionality of PRSS1 gene mutations

Table adapted from (455).

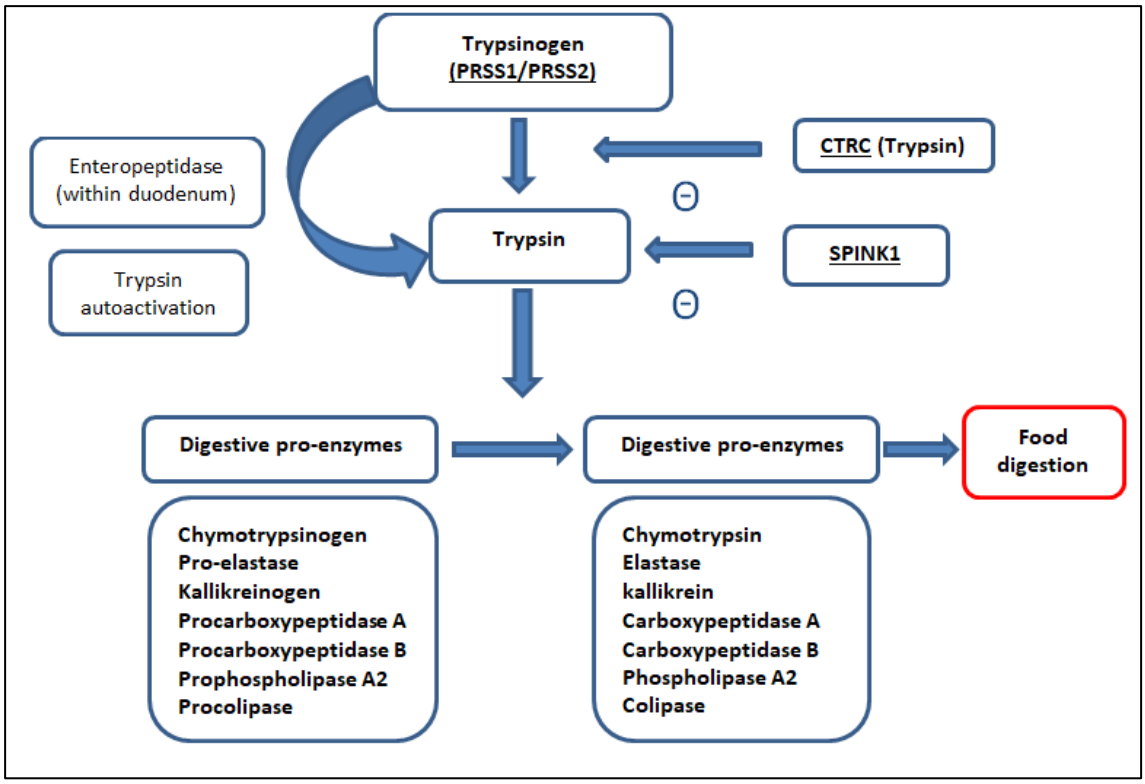

Figure 8.2: Physiology of trypsin

Trypsinogen is secreted by the pancreatic acinar cells and activated to trypsin in the duodenum by the brush border enzyme enteropeptidase. Trypsin is the trigger-enzyme initiating the activation of enzyme cascade of all other digestive proenzymes (described in Chapter 3) as well as trypsinogen itself. Minute amounts of trypsinogen become active within the pancreas and mechanisms which prevent autodigestion the pancreas has two lines of defence which include; trypsin inhibition by SPINK1 (inhibits approximately 20% of trypsin) and trypsin degradation by CTRC. Trypsin itself is needed to further inactivate itself (trypsin catalysed degradation)(462).

(Figure and description adapted from (455))

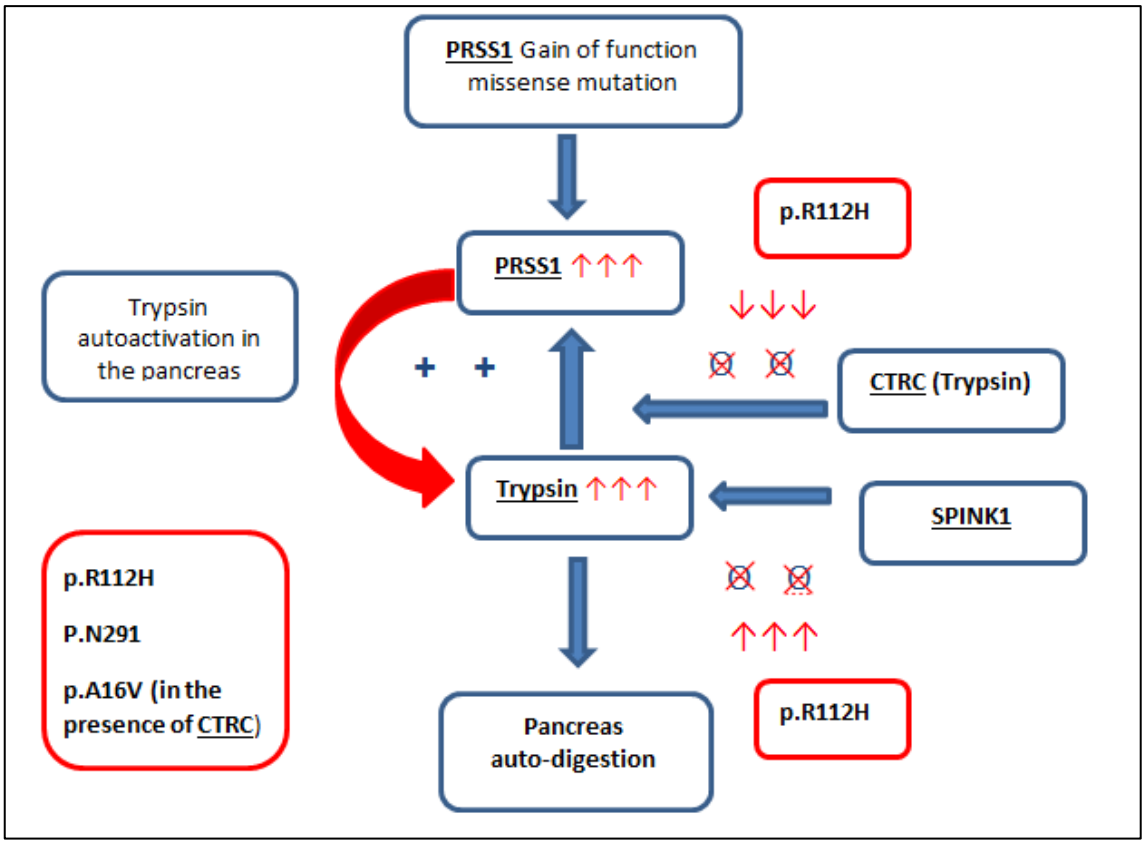

Figure 8.3: Functional consequences of PRSS1 mutations R122H, N29I

Gain-of-function PRSS1 mutations result in an increased amount of trypsin in the pancreas, which facilitates pancreas autodigestion, and thereby chronic pancreatitis. This occurs due to increased stability of PRSS1 enzyme, loss of the lysis site (R122H), increased autoactivation and the retention of activated trypsin.

(Figure and description adapted from (455)).

8.1.3.2. SPINK1 variant N34S and chronic pancreatitis

The pancreatic acinar cells have multiple mechanisms to protect against excess trypsin activation. Failure of these protective mechanisms can lead to the proliferation of active trypsin. *SPINK1* is protein which is secreted by the pancreatic acinar cells and has the capacity to inhibit trypsin. *SPINK1* is synthesised by acinar cells and follows trypsinogen from synthesis to secretion so it is likely to be involved in protecting both acinar cells and the duct from prematurely activated trypsin (101). In contrast to *PRSS1*, *SPINK1* mutations cause damage to the pancreas by producing a loss of inhibitor function.

A landmark study by Witt *et al* (102) examined *SPINK1* mutations in children with idiopathic chronic pancreatitis, and detected the N34S mutation in 23% of patients, (6 homozygous, 12 heterozygous), and found no phenotypic differences between hetero- and homozygous patients. The finding of a *SPINK1* mutation in only a small proportion of unrelated idiopathic chronic pancreatitis patients suggests that other gene mutations play a role in the disease pathogenesis.

A subsequent study also identified an association between *SPINK1* and idiopathic pancreatitis, and again found a high proportion of N34S carriers in the idiopathic pancreatitis cohort (443). The authors also used genetic linkage analysis, and excluded the linkage between hereditary pancreatitis and *SPINK1* mutations (443). This study suggests that *SPINK1* alone is incapable of initiating pancreatitis, and instead acts as a disease modifier which lowers the threshold for pancreatitis or worsens the severity of pancreatitis in conjunction with other environmental or genetic factors. Both *SPINK1* and *CTRC,* though strongly associated with chronic pancreatitis, should be considered as having contributory, rather than causative, roles. Idiopathic chronic pancreatitis is significantly more strongly associated with SPINK1 mutations than alcohol associated disease, therefore suggesting that the cause of idiopathic disease is primarily through a trypsin activation mechanism (236). It is conceivable that *SPINK1* variant N34S may be

important in Irish chronic pancreatitis patients in the context of mutations or carrier status of other susceptibility genes.

8.1.3.3. CFTR variants FR508del and R117H and chronic pancreatitis

As described in Chapter 3, *CFTR* mutations are classified on a molecular level by degree of disruption to *CFTR* protein function. Class I-III variants are considered to be severe, while class IV-V variants are associated with mild or variable dysfunction. Although many mutations in *CFTR* have been reported, the functional implications for many of these mutations have yet to be defined. Specific *CFTR* mutations are significantly associated with pancreatitis. Patients with genotypes which are associated with mild phenotypic effects have a greater risk of developing pancreatitis than patients with genotypes associated with moderate-severe phenotypes (246) (Table 8.2).

CFTR allele	Pancreatitis risk	Example
Severe / mild	High risk, causative	F508del , R117H
Mild / mild	Likely, high risk	R117H , R117H
Severe / -	2.5 fold risk	F508del , -
Mild / -	4 fold risk	R117H , -
Non-CF causing	No risk	
T5	No risk	
TG12	No risk	
T5-TG12	Limited data	

Table 8.2: The effect of known CFTR mutations on the risk of pancreatitis

CF cystic fibrosis, CFTR cystic fibrosis transmembrane conductance regulator gene, T5 allele, TG12 allele, T5-TG12 complex allele

Table adapted with permission from (463)

Cystic fibrosis and chronic pancreatitis are similar in that patients with cystic fibrosis are known to be affected by PEI and episodes of pancreatitis, while some patients with chronic pancreatitis have raised sweat chloride levels (246). Furthermore, in both diseases obstruction in the pancreatic duct occurs due to dense secretions which highlight the link between both entities (464, 465). Cystic fibrosis patients with PEI usually carry two 'severe' *CFTR* mutations, and those who are pancreas sufficient have a severe CFTR mutation compounded by at least one 'mild' variant with some preservation of some *CFTR* function (246). Moreover, pancreas sufficient cystic fibrosis patients with *CFTR* mutations are highly susceptible to pancreatitis attacks and the type and severity of *CFTR* mutation is critical to this risk (246). Therefore, it may be that chronic pancreatitis occurs predominantly in patients who carry 'mild' *CFTR* mutations. The development of chronic pancreatitis requires residual *CFTR* capacity,

and acinar cells, both of which are essential, and may be absent in cystic fibrosis patients with two 'severe' *CFTR* mutations and PEI (226).

It is thought that different types of *CFTR* gene mutations cause varying degrees of impairment and therefore are dissimilar in terms of disease phenotype. Individuals carrying heterozygous severe *CFTR* alleles are *CFTR* cystic fibrosis carriers, which correspond to approximately 3% of the general population in Europe, and *CFTR* mutations represent a major risk factor for the development of idiopathic chronic pancreatitis (466, 467). Studies have validated that there is a strong association between the severity of the *CFTR* genotype and the occurrence of pancreatitis (246). Compound heterozygous genotypes comprising of one severe and one mild or variable *CFTR* allele are strong risk factors for chronic and are considered causative (468). Interestingly, it is mild *CFTR* genotypes that are associated with an increased risk of pancreatitis when compared to the moderate-severe genotypes (246). *CFTR* is one of the most common genetic variants with a carrier frequency of 13% in healthy controls from the American NAPS2 cohort (257). In addition to cystic fibrosis severe, and cystic fibrosis mild phenotypes, there are *CFTR* variants with cystic fibrosis atypical phenotypes that do not cause classic cystic fibrosis but are associated with features of cystic fibrosis such as *CFTR* (severe) and *CFTR* (mild-variable) mutations are associated with CBAVD, recurrent acute and chronic pancreatitis (103, 104, 224, 226, 469). In patients without cystic fibrosis, variants of *CFTR* that inhibit bicarbonate conductance but maintain chloride conductance, may selectively impair secretion of pancreatic juice, leading to trypsin activation and pancreatitis (224)

In patients with idiopathic chronic pancreatitis, *CFTR* gene abnormalities have been reported to occur in approximately 40% of patients (103, 104, 470), and in most cases only one allele is affected. *CFTR* mutations have been found in approximately 15% of alcohol-related chronic pancreatitis patients, and have been associated with less-

functionality of the *CFTR* protein (350). Severe *CFTR* cystic fibrosis causing mutation F508del has been reported with a 7% frequency in patients relative to approximately 3% in healthy controls, and cystic fibrosis-causing mild mutation R117H is reported with a 2% frequency in chronic pancreatitis patients relative to 0.6% in controls (226, 463). *In vitro* and *ex-vitro* studies have provided evidence that high index alcohol consumption impairs *CFTR* function in the duct cells which impairs exocrine function and sensitises the pancreas to disease-causing stimuli (471). Studies have demonstrated that pancreatitis causing insults such as alcohol, smoking and bile acids strongly inhibit *CFTR* function (463). Impairment of *CFTR* function is crucial to pancreatitis development, therefore, patients carrying *CFTR* mutations (in the context of high alcohol intake), may have an increased risk of developing chronic pancreatitis (463, 471).

Although *CFTR* variants have been strongly correlated with pancreatitis, their impact on disease continues to be debated. Analyses from a number of studies have reported unusual variants that do not cause classical cystic fibrosis, but have been identified in pancreatitis. Rosendahl and colleagues propose two terminal positions with regard to associated genes in chronic pancreatitis, which are cystic fibrosis on one side and hereditary chronic pancreatitis on the other (Figure 8.4) (226). In between is complex inherited chronic pancreatitis, including *CFTR*-related disorders, and there may be transition to patients that carry variants in different pancreatitis-associated genes (226). The incidences of non-disease-causing variants are important and must be considered. These variants may also be significant in the context of gene-gene, or gene-environment interactions. Further functional and quantitative research is required to characterise these variants and the mechanisms of disease risk.

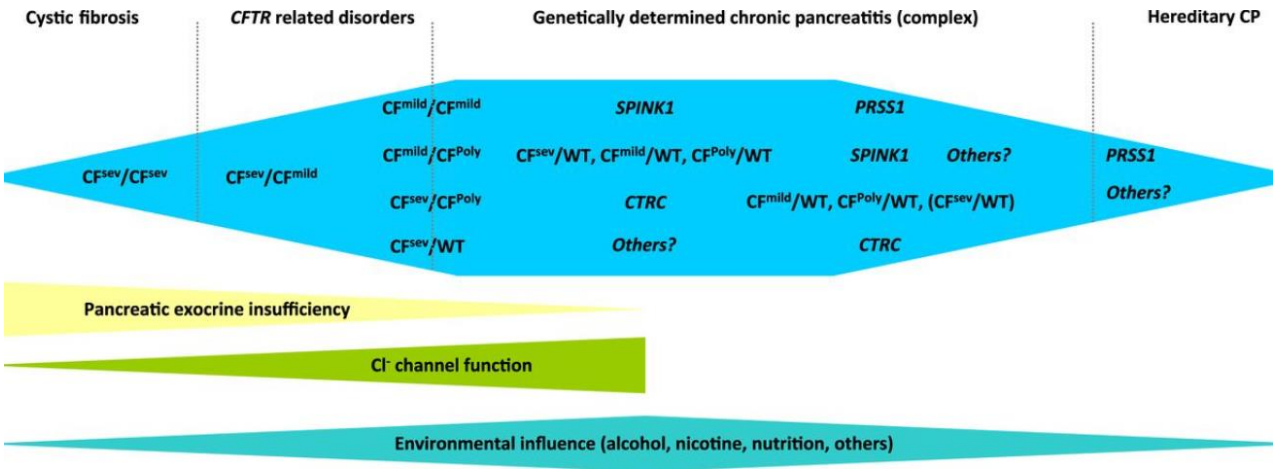

Figure 8.4: Development of chronic pancreatitis through complex genetic and environmental interaction

Cystic fibrosis and hereditary chronic pancreatitis require little or no environmental influence apart from disease-causing genetic basis. Patients with chronic pancreatitis who are compound-heterozygous for CFTR may develop CFTR-related disorders. CFTR function decreases, which is displayed in positive sweat chloride measurements, when CFTR variants accumulate in patients, whereas PEI increases

CF^{sev-} cystic fibrosis causing severe variant; CF^{mild} – cystic fibrosis causing mild variant, CF^{poly} – non cystic fibrosis causing variant

Reproduced with permission (226).

8.1.4. Study rationale

Evidence suggests that patients with chronic pancreatitis may have genetic predisposition to the development of the disease, as well as having environmental stimuli. However there are considerable uncertainties and research gaps. The causative role of pancreatitis-related gene mutations may be of particular relevance amongst idiopathic patients, or amongst those with documented alcohol-related chronic pancreatitis but with apparently modest alcohol consumption. The results of Chapter 6 showed that more patients in Ireland had non-alcohol-related chronic pancreatitis than

had alcohol-related disease. However, Ireland is known to have a moderately high rate of alcohol consumption. The high prevalence of recessive *CFTR*-carriers in Ireland thought to be the highest worldwide, and it is not known whether *CFTR* variants are risk factors in alcohol-related chronic pancreatitis.

Phenotype-genotype analysis will clarify the role of gene variants in Irish chronic pancreatitis patients. Genetic variants are responsible for many clinical factors in chronic pancreatitis, and may alter the course of disease. Identifying and responding to individual patient phenotype, allows for removal of pathogenic factors and more focus on underlying disease mechanisms. The present study was designed to identify the prevalence of mutations in *PRSS1* (R122H, A16V, N29I), *SPINK1* (N34S), and *CFTR* (FR508del, R117H) in an Irish cohort of alcohol-induced and idiopathic chronic pancreatitis patients.

Gene	Variant	Patients	Controls	p Value	OR
PRSS1	R122H	25/660 (3.8%)	0/1758	<0.0001	141.1
	A16V	14/660 (2.1%)	0/1758	<0.0001	78.9
	N29I	8/660 (1.2%)	0/1758	<0.0001	45.8
SPINK1	N34S (hom)	17/660	0/1758	<0.0001	95.6
CFTR	F508del	44/660 (6.7%)	48/1758	<0.0001	2.5
	R117H (7T/7T)	13/660 (2%)	8/1758	0.0009	4.4

Table 8.3: Gene mutation screening panel, showing, gene, variant, frequency amongst patients / controls, p-value and odds ratio (OR)

Mutational screening panel which demonstrates the frequencies of gene mutations in a large German cohort, and which were selected for analysis in the current study. This table shows the frequencies and prevalence of gene variants amongst patients and controls, including P-value (statistically significant <0.05) and odds ratio (OR).

Table reference (226)

8.1.4.1. Study hypothesis

Patients with alcohol-induced and idiopathic chronic pancreatitis have a higher rate of pancreatitis-related genetic mutations than occurs in the general population.

8.1.4.2. Study aim

To aim of this study was to conduct genetic testing for common pancreatic genes mutations in Irish idiopathic and alcohol-induced chronic pancreatitis patients, and to compare the occurrence of pancreatic gene mutations to a historical control database, representative of the general population.

8.1.4.3. Study objectives

(1) To investigate the frequency of major pancreatic gene mutations in a defined cohort of idiopathic and alcohol-induced chronic pancreatitis.
(2) To select a subset of SNPs within candidate genes which are most informative, or due to known or suspected alteration of protein structure or gene regulation
(3) To determine any association between genotypes or the possession of alleles and the disease state

8.2. Methods

8.2.1. Study description

This study had a prospective controlled-cohort design and patients with a diagnosis of idiopathic and alcohol-induced chronic pancreatitis were identified from specialist clinics in the Centre for Pancreatico-Biliary Diseases, Tallaght University Hospital and

St. Vincent's University Hospital (both University-affiliated, tertiary pancreatic referral centres).

The diagnosis of chronic pancreatitis was based on at least two of the following criteria; patient history (abdominal pain typical of pancreatitis), functional deficits (exocrine / endocrine impairment) and/or findings of radiologic / endoscopic studies (computed tomography / endoscopic ultrasonography) and the aetiology were determined precisely by the pancreatic team. Idiopathic aetiology was diagnoses in the absence of other known clinical cause. The aetiology of alcohol-induced chronic pancreatitis was made based on an alcohol intake which exceeded the recommended intakes and in the absence of other clinical causes. All abdominal imaging and endoscopic examinations were reviewed to evaluate pancreatic morphology. The medical records of all patients were reviewed for demographic and clinical data.

8.2.1.1. Patient recruitment

Patients with a diagnosis of idiopathic or alcohol-induced chronic pancreatitis were identified as eligible for study inclusion through discussion with consultant specialists and through attendance at specialist pancreatic clinics. One hundred and twenty six patients with idiopathic or alcohol-induced chronic pancreatitis were recruited for study. Patients were excluded is they had a diagnosis of cystic fibrosis, a family history of hereditary pancreatitis, if they were pregnant, if they were less than 18 years of age, or if they were unable to provide informed written consent. All patients were offered genetic counselling prior to inclusion in the study. Patients were made aware that the presence of a mutation would not predict the course of the disease, nor would it affect clinical management and patients were made aware that further genetic counselling would be available and arranged for patients depending on the outcome of testing. All patients were offered genetic testing and underwent genetic testing for the specified variant mutations of *PRSS1*, *SPINK1* and *CFTR*.

The medical records of all patients were evaluated, and patients were assessed for the following clinical indices: personal or family history of pancreatitis, smoking status (pack-year), history of alcohol consumption, history of acute pancreatitis, age of onset of chronic pancreatitis, diagnosis, medical and surgical history, and medications.

8.2.1.2. Control recruitment

Controls subjects were sought from an anonymous historical control database which is held in the Institute of Molecular Medicine, St James's Hospital, Dublin 8. This control database includes 2,047 healthy persons, without disease, who are representative of the general population. The DNA was extracted following informed consent from persons attending the Irish Blood Transfusion Service for blood donation. In total, 167 controls from the control database were included in the current analysis, and were randomly selected from the database. Age and gender of the controls were known, and no other clinical or socio-economic characteristics were available.

8.2.1.3. Statistical analysis

Statistical analysis was conducted using SPSS Version 22 (SPSS, Chicago, IL, USA, 2015). Data were compared by means of Fisher's exact test, and the Chi square test were used for categorical data. Continuous variables were analysed using a Student's *t* test for independent samples. A *P* value of <0.05 was considered statistically significant.

8.2.1.4. Ethical approval

This study had full ethical approval from the Tallaght University Hospital / St James's Hospital Joint Research Ethics Committee (JREC) (Ref 2015-03) and St. Vincent's University Hospital Research Ethics Committee (Appendix B).

8.2.1.5. DNA extraction

DNA was extracted manually from whole blood samples at the Trinity Biobank, and the protocol was based on Gentra technology (manual DNA extraction as per local policy Appendix R). At the end of the process, the DNA was stored in the supplied in TE buffer solution, at -20ºC or -80ºC for long term storage. DNA was extracted from blood samples of 126 patients.

8.2.1.6. TaqMan method

TaqMan assays were performed in accordance with Applied Biosystems *TaqMan® SNP Genotyping Assays protocol* (Part Number 4332856 Rev. D, 07/2010).
DNA samples were diluted to a concentration of 2ng/µl in purified, DNase free water.
Reaction master mixes were prepared to distribute the following contents per assay:
10µl TaqMan Genotyping PCR Master Mix (2✕).
4.5µl purified, DNase free water.
0.5ul genotyping assay primer/probe (40x).

To a 96-well PCR plate, 15µl of the above master mix was transferred to each well, followed by 5ul of the prepared diluted DNA which was applied in singlicate. A negative control (purified, DNase free water) was used in place of DNA to a single well of each

plate. Plates were then tapped gently to bring contents to the bottom of wells and sealed with an optical adhesive film.

Each plate was subjected to a PCR amplification cycle with the following settings:

10 min hold at 95°C, 40 cycles: 15 seconds at 92°C (denaturation), 60 seconds at 60°C (annealing and extension). The ABI 7500 thermocycler was set to read VIC/FAM as a genotyping assay. End point reads were used to determine genotype.

Sample analysis was conducted by a genomic scientist in the Institute of Molecular Medicine, St James's Hospital Dublin, under the supervision of the Professor of Molecular Medicine, who was a collaborator in this study.

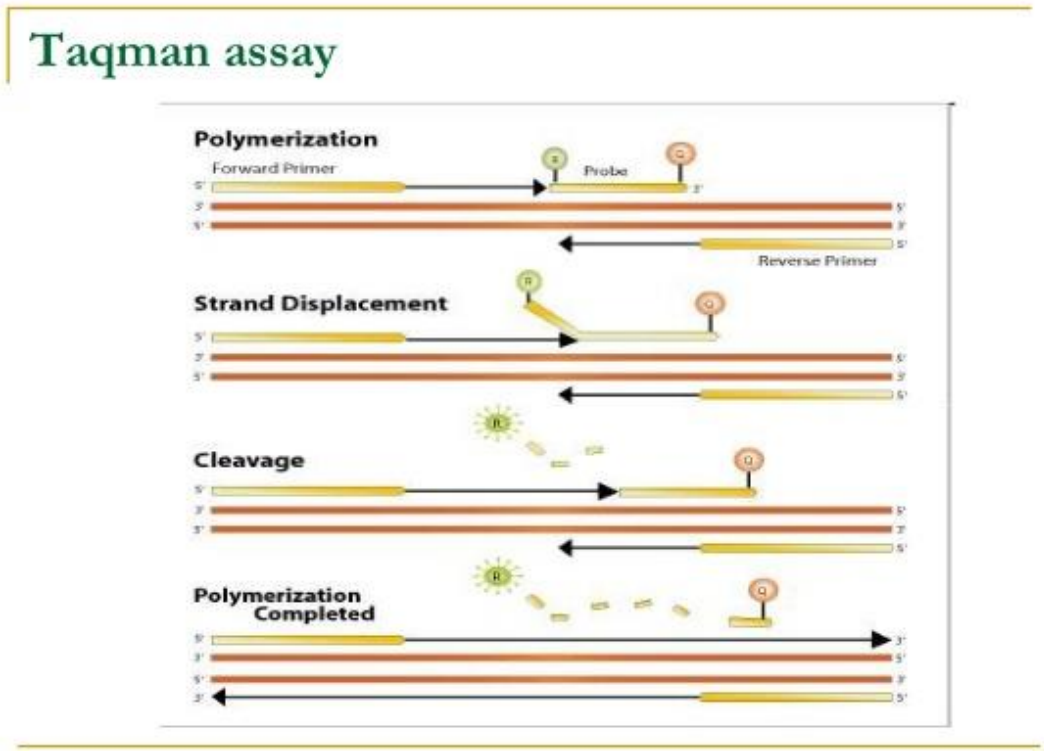

Figure 8.5: An overview of the TaqMan genotyping technology showing the four main stages of the process

8.3. Results

8.3.1. Patient characteristics

A total of 126 patients were evaluated for the presence of *PRSS1*, *SPINK1* and *CFTR* mutations and the clinical characteristics are detailed on Table 8.4. Most patients were male (67.4%) and the mean (standard deviation, SD) age was 55.04 (12.2) years.

Of the 126 patients, 54.8% (n=69) had an alcohol-aetiology and 45.2% (n=57) had an idiopathic aetiology. Over half of patients did not have diabetes (59.5%, n=75). With regards to smoking, 49.2% (n=62) were current smokers, and 27.0% (n=34) were never smokers. In terms of alcohol use, 47.6% (n=60) drank alcohol, 43.7% (n=55) reported being ex-alcohol drinkers and 8.7% (n=11) reported never drinking alcohol. The majority of patients (73.0%, n=92) were pancreatic insufficient (Table 8.4).

8.3.2. Control age and gender

One hundred and sixty seven controls were included in the analysis, the majority were female (54.5%) and the mean (SD) age was 40.88 (14.09) (P=0.000) (Table 8.4).

8.3.3. Group analysis

Mutations in *CFTR* / *SPINK1* occurred in more patients with chronic pancreatitis (19.8%) than in the control group (6.0%) (P=<0.0001). Mutation analysis for *CFTR* / *SPINK1* showed a 3.88 fold increased risk for patients with chronic pancreatitis compared to controls (P=<0.0001). Mutations in *SPINK1* showed an odds ratio (OR) of

5.92 (95% CI 1.93-18.2) (P=0.001) demonstrating that patients with chronic pancreatitis are greater than 5 times more likely to have a *SPINK1* genetic mutation than historic controls. Patients were not statistically more likely to have a *CFTR* genetic mutations F508del (P=0.649) and R117H (P=0.193) than controls. There was no age difference between patients and controls bearing mutations (P=0.158). Similarly there was no difference in gender in those testing positive or negative for gene mutation (P=0.135). PRSS1 mutations were present in neither patients nor controls (Table 8.5). One patient was trans-heterozygous for *SPINK1* N34S and *CFTR* F508del. However, as this only occurred in one patient, it was not possible to identify if the variants had a synergistic, additive, or counter-neutralising effect.

8.3.4. Mutational analysis of PRSS1

Analysis of the cationic trypsinogen gene revealed that there were no mutations in patients with chronic pancreatitis patients of either aetiology, or amongst the control group. Mutations in R122H, A16V and N29I were absent from both the chronic pancreatitis group and the control group.

8.3.5. Mutational analysis of SPINK1

Mutational analysis of *SPINK1* N34S in patients with chronic pancreatitis and controls was performed. Sixteen individuals with chronic pancreatitis (12.7%) and four controls were heterozygous for the N34S mutation (P=0.001). Among chronic pancreatitis patients, the N34S mutation was detected in the heterozygous form in nine (56.3%) patients with alcohol-induced disease, and in seven (43.8%) patients with idiopathic disease (P=0.977). The odds ratio (OR) for the occurrence of N34S mutation in patients with chronic pancreatitis was 5.93 (95% CI) (1.93-18.1).

Secondary analysis of *SPINK1* N34S was conducted and the control population was increased to n=508. Additional mutations were not detected amongst the control cohort and N34s mutations were significantly more present in patients (12.75 (n=126) than controls (2.4% (n=508)(P=0.0000005) (Table 8.6).

8.3.6. Mutational analysis of CFTR

CFTR mutational analysis revealed F508del heterozygous mutations in five (4.2%) chronic pancreatitis patients and five (0.2%) controls (P=0.746). One patient with idiopathic chronic pancreatitis and four patients with alcohol induced chronic pancreatitis were heterozygote for F508del (P=0.746). *CFTR* mutational analysis revealed R117H mutations in three patients (2.5%) and one control (0.05%) (P=0.169). Mutation of R117H occurred in more patients than controls (2.5% vs <1%) but this did not reach significance (P=0.169).

Characteristics	Patients (n=126)	Controls (n=167)	P-value
Age in years, mean (SD)	55.04 (12.2)	40.88 (14.09)	0.000*
Sex M:F	85:41	76:91	0.000*
Aetiology			
Alcohol	69 (54.8)	-	
idiopathic	57 (45.2)		
Diabetes mellitus n (%)			
Yes	51 (40.5)	-	
No	75 (59.5)		
Smoking n (%)			
Yes	62 (49.2)	-	
Ex	30 (23.8)		
Never	34 (27.0)		
Alcohol use			
Yes	60 (47.6)	-	
Ex	55 (43.7)		
Never	11 (8.7)		
Pancreatic exocrine insufficiency n (%)			
Yes	92 (73.0)	-	
No	34 (27.0)		

Table 8.4: Characteristics of patients who were tested for pancreatic gene mutations

Pancreatic exocrine insufficiency was based on results from Faecal Elastase-1 test

**Statistically significant <0.05*

Chi squared test used

	Patients (n=126)	Controls (n=167)	P-Value	Odds ratio (OR)	95% Confidence interval
Any mutation n (%)	25 (19.8)#	10 (6.0)	0.000*	3.886	1.79 – 8.43
SPINK1 n (%)					
N34S	16 (12.7)#	4 (2.4)	0.001*	5.927	1.93 – 18.1
CFTR n (%)					
F508del	5 (4.0)#	5 (3.0)	0.649	1.339	0.379 – 4.72
R117H	3 (2.4)	1 (<1)	0.193	4.049	0.416 – 39.9
PRSS1 n (%)					
R122H	0	0	N/A	-	-
N29I	0	0	N/A	-	-
A16V	0	0	N/A	-	-

Table 8.5: Distribution of SPINK1, CFTR, PRSS1 mutations in chronic pancreatitis patients and historic controls

**Statistically significant <0.05*

 # One patient was transheterozygous for N34S and F508del

Chi squared test used

SPINK1 N34S			
Total Controls	508	Total Patients	126
Controls without variant	496	Patients without variant	110
Controls heterozygous	12	Patients heterozygous	16
Controls homozygous	0	Patients homozygous	0
Controls indeterminate	0	Patients indeterminate	0
	2.4%		12.7%
	P=0.0000005		

Table 8.6 Secondary analysis of SPINK1 N34S including additional controls

	Any positive mutation	No positive mutations	P-Value
Total positive and negative patients & controls n (%)	35	258	0.000*
Age years (mean,SD)	49.70 (11.99)	46.59 (15.38)	0.158
Sex (Male:Female)	20:5	65:36	0.135
Aetiology Alcohol idiopathic	 15 (42.9) 10 (28.6)	 54 (42.8) 47 (37.3)	0.557
Smoking, n (%) Yes No	 13 (37.1) 12 (34.3)	 51 (40.5) 50 (39.7)	0.893
Alcohol, n (%) Yes No	 24 (68.6) 1 (2.9)	 91 (72.2) 10 (7.9)	0.349
Diabetes mellitus, n (%) Yes No	 10 (28.6) 15 (42.9)	 41 (32.5) 60 (47.6)	0.063
Pancreatic exocrine insufficiency, n (%) Yes No	 15 (42.9) 10 (28.6)	 77 (61.1) 24 (19.0)	0.101

Table 8.7: A comparison of clinical and demographic characteristics between patients who had at least one ('any') positive genetic mutation (SPINK1, CFTR, PRSS1) and patients who had no positive genetic mutations

**Statistically significant P<0.05*

#Chi squared test used

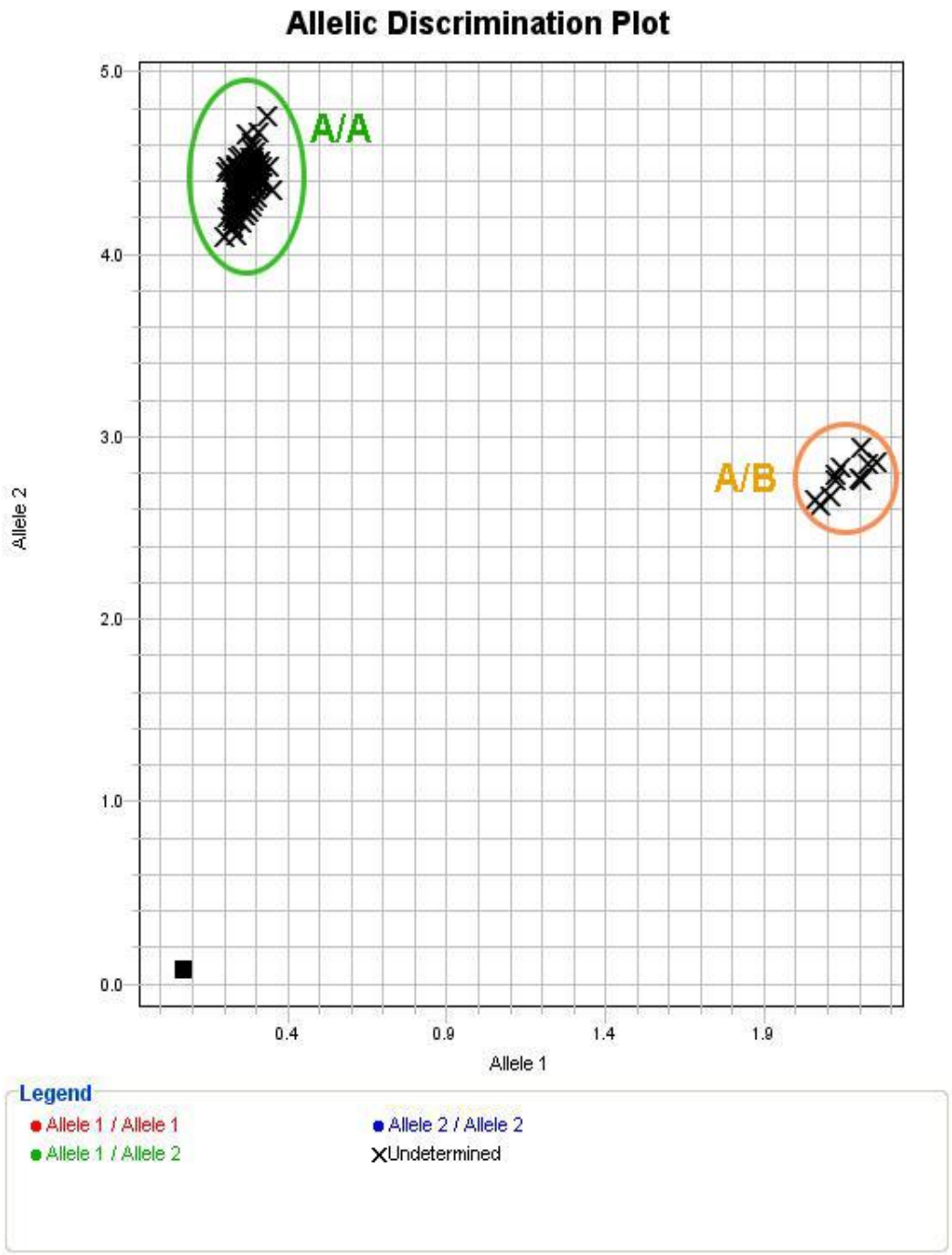

Figure 8.6: Amplification pattern of SPINK1 variant N34S (rs17107315) genotyping by PCR with TaqMan SNP genotyping assay

**PCR – polymerase chain reaction, SNP – single nucleotide polymorphism*

A/A represents Homozygous normal
A/B represents Heterozygous
B/B (not present) represents Homozygous

8.4. Discussion

This present study aimed to determine if Irish idiopathic and alcohol-associated chronic pancreatitis patients in Ireland were more likely than controls to harbour pathogenic genetic variants. Close to 20% of the chronic pancreatitis cohort had disease-associated mutations. The results indicate that the presence of pancreatic gene mutations in chronic pancreatitis patients increases their risk of disease by more than three-fold. Importantly, the presence of a heterozygous N34S allele, known to be a disease modifier, confers a five-fold increased risk of chronic pancreatitis when compared to healthy controls. Mutated N34S is thought to occur in approximately 1% of the general population and increases disease risk almost 20-fold (252, 443). In agreement with studies conducted worldwide, this provides further evidence of the frequency of chronic pancreatitis mutations, thought to increase susceptibility to pancreatic injury and associated disease. The three genes in the mutation screening panel are mechanistically linked to the control of trypsin activity within the pancreas. *SPINK1* is linked to trypsin as a specific trypsin inhibitor, and *CFTR* as a ductal anion channel responsible for generation of fluid secretion which flushes prematurely activated trypsin in the ducts out of the pancreas. *PRSS1* gene mutations are thought to prevent the inactivation of trypsin within the pancreas, which leads to pancreatic autodigestion and subsequent pancreatitis. In agreement with studies conducted worldwide, this study provides further support of the frequency of chronic pancreatitis mutations, thought to increase susceptibility to pancreatic injury and associated disease. The diagnosis of chronic pancreatitis is classified according to epidemiologic risk factors including family history, smoking and alcohol use, although the relative risk of an environmental factor may be minor (63, 273). If no inciting factor can be established, patients are diagnosed with idiopathic disease which has two distinct sub-types (early and late) distinguished by age of onset. As already mentioned alcohol is considered a major risk factor for pancreatitis development, despite reports that fewer

than 5% of alcoholics develop pancreatitis suggesting that other risk factors are also important to disease pathogenesis (95). Many patients with chronic pancreatitis do not consume alcohol (472), as evidenced in the current study with 7% of patients reporting lifelong abstinence. There are distinct genetic variants which can affect each of the factors which lead to chronic pancreatitis, and which can alter the course of pancreatic disease (101, 473). Identifying and responding to knowledge of these factors represents a step towards removing key pathogenic factors and focuses on the underlying mechanism of risk (473). The key concepts of the presentation and clinical course of chronic pancreatitis are that the onset, severity, complications, and rate of progression are unpredictable (219). Furthermore, the pathological pathways from healthy pancreas to end-stage pathology of pancreatitis are not clearly defined. However, research has helped to provide insight into certain aspects of the mechanisms of pancreatic injury which lead to chronic pancreatitis.

The study methodology using commercially available genetic testing, only evaluated the selected variants on the three genes of interest, therefore, many pathogenic negative patents may harbour gene variants which are not assessed using this method, and therefore not evaluated in this study. Furthermore, it is likely that there are other genetic or environmental factors which alone, or in combination, result in or influence the development of chronic pancreatitis (474). The diagnostic yield of almost 18% in patients with chronic pancreatitis may in fact be higher, given that in the other 82% of patients of patients in the study may have genetic variants that have not been tested.

8.4.1. PRSS1

Three years after the identification of *PRSS1* as a causative agent of hereditary pancreatitis (51), gain-of-function *PRSS1* mutations were first reported in patients with idiopathic chronic pancreatitis in 1999 (223, 238). The prototype susceptibility factor *PRSS1* with two well established gain-of-function variants, N29I and R122H are known

to lead to hereditary pancreatitis. Hereditary pancreatitis which is an autosomal dominant Mendelian disorder is characterised by recurrent episodes of acute pancreatitis, with only a subset of patients progressing to classic chronic pancreatitis, which usually occurs many years after the initial acute episode (450). In addition to gain-of-function missense mutations, gain-of-function *PRSS1* gene duplication and triplication copy number mutations in idiopathic chronic pancreatitis patients were reported in 2008 (475). The pathogenic variants of *PRSS1* are not commonly found in the general population and have only been reported with minute frequency (0.003% and 0-0.3%) (105, 476). *PRSS1* mutations which are typically associated with hereditary pancreatitis (51), notably mutations R122H, N29I, A16V R122c and D22G have also been observed in other groups of recurrent acute and chronic pancreatitis patients (220, 238, 476, 477). Furthermore, *PRSS1* gene mutations have been reported in variable rates in chronic pancreatitis patients of idiopathic aetiology (0-21%) (238, 469, 478, 479). Witt and colleagues reported a 10% prevalence of mutated A16V in idiopathic patients who lacked a family history of pancreatitis (223). The authors suggested that genetic testing should be undertaken even in the absence of family history of disease as a significant number of idiopathic patients may have a genetic basis to their disease (223). Patients with the three most common *PRSS1* mutations, R122H, N29I and A16V are thought to be phenotypically similar with no significant difference between each mutation, and in those without *PRSS1* mutations (456). The current study examined the presence of three common *PRSS1* mutations (N29I, R122H, A16V) in patients with pancreatitis and healthy controls. No *PRSS1* mutant variants were found in patients or controls. The analysis was conducted by a Professor of Molecular Genomics, and though satisfied that the assay functioned, caution must be exercised when interpreting the results due to non-validation of the control assays.

However, *PRSS1* mutations have not reported in chronic pancreatitis patients in a number of countries, which is in agreement with the current study findings of no mutation prevalence amongst patients or controls. A recent systematic review and

meta-analysis examined the role of PRSS1 R122H and the risk for chronic pancreatitis in non-hereditary and hereditary patients (480). The authors reported that R122H is strongly associated with chronic pancreatitis, particularly hereditary forms, however it is not associated with non-hereditary forms including alcoholic and idiopathic chronic pancreatitis (480). In the UK O'Reilly *et al* (478) found a R122H mutation in one patient with alcoholic disease, but N29I and A16V were not present in any patients. This finding was replicated in German chronic pancreatitis patients of alcohol-associated disease where N29I and R122H were not found amongst patients (481). An absence of *PRSS1* mutations in patients with alcohol-related aetiology has been reported in studies from the USA (482), India (483), the Netherlands (484) suggesting that PRSS1 mutations may not be common predisposing risk factors amongst alcoholic patients. However *PRSS1* mutations have been reported in frequencies of 1.5%-33% amongst alcohol-related pancreatitis patients from Brazil and Poland (479, 485). Reported variations in trypsinogen frequency amongst patients with alcohol-associated and idiopathic disease may be explained by genetic diversity in different ethnic groups.

In one of the highest reports from Europe, *PRSS1* mutations R122H and N29I were found in 21% Polish idiopathic chronic pancreatitis patients, which was significantly higher than the control group (4.3%) (479). There was no evidence of family history of chronic pancreatitis or pancreas cancer (479). Further, R122H mutations were reported in 10% of German idiopathic chronic pancreatitis patients, and the authors noted that disease onset occurred at a significantly younger age in those with, than in those without, *PRSS1* mutations (486). A Japanese study examined *PRSS1* mutations in patients with a family history of pancreatitis or early-onset (<40 years of age) idiopathic recurrent acute or chronic pancreatitis (451) and R122H and N29I mutations were present in 43.9% of the cohort. Based on the findings the authors revised the criteria for the diagnosis of hereditary pancreatitis to include recurrent acute and chronic pancreatitis patients with R122H or N29I mutations (451). In the largest examination of

PRSS1 mutations in hereditary chronic pancreatitis (450) an interesting finding was that 19% of families had clinical manifestations of disease indistinguishable from mutation positive patients, outlining the potential importance of other genes in the pathogenesis of pancreatitis (450).

A recent large genome-wide association study in alcohol-associated chronic pancreatitis patients in the US discovered that common variants in the *PRSS1-PRSS2* locus was associated with an increased risk of alcoholic and sporadic pancreatitis (274). Specifically, a *PRSS1-PRSS2* variant was found to protect against chronic pancreatitis, and another increased disease susceptibility (274). Rare *PRSS1* variants (R122H, A16V) were also analysed and are reportedly independent with the observed phenotype in the cohort (274). This finding has been replicated independently in a large European cohort (351). These studies highlight the importance of sustained investigations of gene-associated variants. Further functional studies are required to establish the effect of hereditary-pancreatitis associated mutations in chronic pancreatitis patients, as well as their contribution to the pathogenic mechanisms of pancreatic injury. Although mutations of *PRSS1* have been implicated in hereditary and less frequently in non-hereditary forms of chronic pancreatitis, the presence and contribution of other genes, epistasis, and environmental factors is important, and remains to be elucidated.

8.4.2. SPINK1

In the present study, the prevalence of *SPINK1* N34S in patients with chronic pancreatitis from Ireland was almost 15%. It was further demonstrated that the prevalence of *SPINK1* N34S is higher than what is predicted to be normal prevalence in the general population. Therefore, this data highlights that substantial numbers of patients who are categorised as having ‘idiopathic’ (or in fact, alcohol-related) disease,

may in fact be genetically susceptible to the disease, in the presence of some environmental risk factor. Therefore, the definition of idiopathic chronic pancreatitis requires reconsideration, and arguably, should only be considered after the exclusion of possible common genetic associations.

The *SPINK1* gene protects pancreas cells against prematurely activated trypsin, and mutations in the gene, particularly the N34S mutation seems to be associated with chronic pancreatitis (102, 222, 443). The N34S gene variation is thought to result in decreased inhibitory capacity in the pancreas resulting in damage (102, 222, 443). *SPINK1* mutations are found in about 1-3% of the general population (443). Idiopathic chronic pancreatitis is strongly associated with the common *SPINK1* high-risk haplotype N34S (236). A series of meta-analyses were conducted to test the hypothesis that *SPINK1* mutations were stronger risk factors in the case of chronic pancreatitis resulting from recurrent trypsin activation than they were in alcohol or smoking related disease (236). The authors underlined the small effect of N34S in alcohol-related chronic pancreatitis patients suggesting that alcohol's primary effects are largely driven through a non-trypsin related pathway (236). The results of this study also suggest that large effect sizes of *SPINK1* N34S in small genetic cohorts may be related to several different, complex, multi-step aetiological pathways leading to the same clinical endpoint (224). This suggests that genetic factors which may be critical in one aetiology pathway will only be shown to have a large effect in populations in which that pathway dominates (236, 487, 488). A second recent meta-analysis on the role of *SPINK1* variant in European chronic pancreatitis patients reconfirmed the strong association, and N34S increases the overall risk of disease nine-fold (489). The authors found the association of *SPINK1* N34S to be more than two-fold higher in idiopathic than alcohol-related patients. The risk of alcoholic chronic pancreatitis is five times higher in the presence of N34S mutation (489), and this may be due to the non-trypsin mediated mechanism of alcohol, driving the disease. This meta-analysis also highlighted a dose effect of a variant as a risk factor for disease, those carrying

homozygous mutated genotype share a higher OR than those carrying a single mutated allele (97.7 *vs* 6.8) (489). These data confirm the association of *SPINK1* N34S and chronic pancreatitis, although it is insufficient to cause disease in isolation, it increases risk in the presence of other risk factors or other gene mutations (489).

A high incidence of *CFTR* mutations has been reported patients with idiopathic chronic pancreatitis, furthermore, the combined risk of *CFTR* and *SPINK1* mutations has been shown to be multiplicative rather than additive (252). In two studies on patients with idiopathic chronic pancreatitis with clinical features of cystic fibrosis, the combination of trans-heterozygous *CFTR* and *SPINK1* variants markedly increased the risk of pancreatitis (224, 252). Schneider *et al* (224) demonstrated for the first time a very high risk of pancreatitis in patients with specific *CFTR* mutations (R75Q, F508del) and showed that *CFTR* bicarbonate conductance is specifically impaired in the relatively common *CFTR* variant R75Q. These studies clearly establish that there are differences in the effect of *SPINK1* in different disease aetiologies. Furthermore, the effects of combinations of gene mutations are important to disease pathogenesis. The presence of *SPINK1* mutations are thought to predispose patients to an earlier disease onset (490). Moreover, although chronic pancreatitis has a known increased susceptibility to pancreatic cancer, an epidemiological report from Japan reported that the presence of *SPINK1* N34S in chronic pancreatitis patients may be viewed as a predictor for pancreatic cancer (491). However, this important finding requires further study.

In the current study N34S mutation in heterozygous form occurred more often in alcohol-associated patients. The presence of N34S in supposedly trypsin-independent disease may highlight to factors; the misclassification of idiopathic patients into alcohol-aetiology, or, an increased susceptibility to alcohol or environmental damage amongst heterozygous patients. However many studies have not reported the phenotype-genotype correlations in idiopathic and alcohol-induced patients who are test positive for N34S mutations, and additional knowledge is required. Again further studies are

warranted to further assess the factors which may confound or modify disease risk. There is also need to quantify the pathophysiologic mechanisms involved, and their implications on disease.

8.4.3. CFTR

As detailed in Chapter 3, *CFTR* is an anion channel and therefore allows the movement of either chloride or bicarbonate across the duct lumen from inside the duct (in which it is responsible for increasing pH and initiating and driving pancreatic juice) (219). The presence of two severe deleterious *CFTR* alleles (e.g. F508del homozygotes) is necessary to give rise to cystic fibrosis, and heterozygosity for such an allele is sufficient to confer increased risk of idiopathic chronic pancreatitis (466, 467). Compound heterozygosity involving a severe *CFTR* allele plus a less deleterious ('mild' or variable') allele (e.g. F508del / pR117H) confers a further increased risk (466, 467). Compound heterozygosity for two mild *CFTR* mutant alleles, is rare and probably increases pancreatitis risk strongly, but to date solid data are lacking (463). Research has shown that patients with exocrine insufficiency in most cases carry two 'severe' *CFTR* variants, and patients with sufficient exocrine function carry at least one 'mild' *CFTR* variant (246). The hypothesis is that the risk of pancreatitis is related to the degree of pancreatic acinar preservation and severity of ductal obstruction which are both associated, but in opposing directions with the severity of *CFTR* dysfunction (246).

The current study examined the prevalence of the most commonly seen *CFTR* (severe and mild) mutations in idiopathic and alcohol-induced chronic pancreatitis patients. Results demonstrated that heterozygous F508del only marginally more enriched amongst patients with chronic pancreatitis (4.2%) relative to controls (0.2%) but this did not reach significance, and this finding is dissimilar to the literature (448). Therefore, cystic-fibrosis carrier status in the current study conferred only a small increased risk

for chronic pancreatitis (OR 1.4). Mild *CFTR* mutation R117H was slightly more prevalent in patients with chronic pancreatitis when compared to controls (2.5% *vs* 0.006%), but again did not reach significance. The results of the current study indicate that the frequency of *CFTR* variants is less pronounced than previously reported with odds ratios between <0.06%-4.2%. The largest examination of *CFTR* variants in idiopathic and hereditary patients yielded similar results, and the authors suggest that influence of *CFTR* in the pathogenesis of chronic pancreatitis has so far been overestimated (226). The relationship between *CFTR* variants and chronic pancreatitis is well established; however the classification of variants with regard to their influence on the development and the risk increase for carriers has not been comprehensively defined (226).One obstacle to comprehensive *CFTR* sequencing is the large 27-exon spanning gene size, with more than 1600 mutations and 200 polymorphisms already reported, many of which have not been completely studied or classified, and especially in consideration of the potential effects on pancreatic duct cells and phenotypes (224). A recently published consensus statement details the clinical consequence of some *CFTR* variants and their association with pancreatic exocrine function have been classified (492). This study which examined only two common *CFTR* mutations in a cohort of 126 patients and 167 controls therefore was not designed to detect the presence of rare mutations with unknown clinical context. Although genotype / phenotype associations are useful for genetic epidemiological studies and patient-specific risk factor education, *CFTR* genotype does not accurately predict individual outcome (492).

The study findings have important implication patient testing and diagnosis. It appears that the risk of pancreatitis in the context of a *CFTR* mutation appears to be high regardless of the type of mutation. Pelletier *et al* found double the amount of chronic pancreatitis patients who were heterozygotes than compound homozygotes, suggesting that one copy of an abnormal *CFTR* allele is enough to predispose to

pancreatitis (493). Cavestro *et al* (448) found *CFTR* mutations in 5.6% (8/142) of their Italian cohort, and all patients were heterozygous for the F508del variant. Similarly having a compound heterozygous genotype does not appear to confer an increased pancreatitis risk, in comparison to chronic pancreatitis with a single allele mutation (252).

Consensus of the role of *CFTR* variants has been strengthened by full gene sequencing in three recently published large scale studies from France (468), Germany (226) and USA (257). In a French study comprehensive screening analysis of *PRSS1*, *SPINK1 CFTR* and *CTRC* found that *CFTR* genotypes contributed to or caused idiopathic chronic pancreatitis in 24% of patients (468). The overall assessment of patients on an individualised based including the effect of epistatic interactions on the disease risk is pre-requisite to understanding the genotype-phenotype profile of complex idiopathic chronic pancreatitis (468). The prevalence of *CFTR* compound heterozygotes in the French study was 2.5%, slightly higher than the 1.4% reported in a large German cohort of idiopathic or hereditary chronic pancreatitis patients (226).

An important study in 2010, demonstrated that active 'with-no-K' lysine kinase (WNK1 with SPAK) is responsible for a change in *CFTR*, from a chloride to a bicarbonate conducting channel (253). *CFTR* conductance of bicarbonate is essential for pancreatic function, as well as the function of other organs. This led to the consideration that *CFTR* variant that disrupt the 'WNK-SPAK' pathway and reduce bicarbonate conductance, may increase the risk of pancreatitis, and also affect other organs which utilise bicarbonate for conductance (257). This led to the large NAPS2 cohort study, which included 984 well-phenotyped patients, and reported 9 rare *CFTR* variants not typically associated with lung disease, but associated with mechanisms altering bicarbonate conductance (257). Therefore, mutated *CFTR* channels secrete chloride (important for lung, sweat glands and intestines), but not bicarbonate, which is

important in the pancreas, sinuses and the male reproductive organs. In this study patients with any of the 9 new *CFTR* variants had chronic pancreatitis, sinusitis and male infertility, but without the chloride-dependent pathology of cystic fibrosis (257). Taken together these studies further strengthen the complexity of *CFTR* dysfunction in pancreatic diseases.

It was recently reported by Schneider *et al* (224) that the assumed benign variant *CFTR* R75Q is associated with familial and sporadic chronic pancreatitis, either with another recessive *CFTR* variant or with *SPINK1* N34S haplotype. This study showed that there was normal chloride conductance, but a selective disruption in bicarbonate conductance, indicating that *CFTR* R75Q causes selective bicarbonate defective ($CFTR^{BD}$) conductance and is associated with chronic pancreatitis but not cystic fibrosis (224). This study demonstrated that R75Q alters bicarbonate but not chloride conductance (224). This is consistent with a chronic pancreatitis model that recognises *CFTR* as pancreatic duct cell bicarbonate channel and predicts that *CFTR* mutations disrupting bicarbonate conductance will markedly increase risk of pancreatic disease either through total disruption of protein processing (e.g. F508del) or alteration of channel properties (e.g. R75Q)((224, 494). In the current study the decision was taken to exclude R75Q from analysis in this cohort, as it is thought to be similarly distributed between patients and controls. However, there is compelling evidence of epistasis of these aforementioned genes and mutant variants, and these require further study including the genotype-phenotype consequences for chronic pancreatitis.

8.4.4. Clinical applicability of genetic study findings

The evaluation of genetic mutations is important to identify the mechanistic aetiology of disease. Genetic risk factors for pancreatitis susceptibility and complications have

vastly different consequences and therefore require an individualised approach to management. Variants in *CFTR*, *SPINK1*, *PRSS1* and others result in complex genotypes, within or beyond the context of alcohol or smoking. Interpretation of genes, variants, and context may be critical to immediately defining the reason for pancreatitis susceptibility and disease progression thereby limiting continued expensive and invasive evaluations or preventative procedures (495). Genetic testing provides clear answers to nonspecific signs and symptoms of pancreatic diseases which allows for a focus on correct diagnosis.

Each episode of acute pancreatitis has serious potential medical and surgical consequences and recurrent episodes of acute pancreatitis confer a significant risk to the development of chronic pancreatitis. The early identification of pathogenic variants can be valuable in clinical practice. If patients are identified early in the disease, aggressive risk factor modification such as counselling for alcohol intake and smoking cessation may prevent the progression to chronic pancreatitis, and further reduce the risk of pancreas cancer (449, 496, 497). Furthermore, the identification of pathogenic variants may reduce the possibly misdiagnosis of alcoholic chronic pancreatitis, and the associated negative stigma which is attached to this diagnosis.

The chronic pancreatitis cohort used in the study was representative of patients seen routinely in clinical practice in a tertiary pancreatic specialist service. Alcohol consumption is associated with 60-70% of disease in developed countries, while 30% of cases are thought to be idiopathic (136). The diagnostic yield of 17.8% is an important consideration in clinical practice, and diagnostic guidelines should be extended to include genetic diagnosis, as the presence of pancreatitis associated gene mutations may be an important basis of disease in a number of patients.

8.4.5. Personalised approach to genetic disorders

Genetic testing is fundamental to the understanding and the management of complex disorders and is the cornerstone of the personalised medicine approach (498). Treatment and management strategies for chronic pancreatitis are designed to improve signs and symptoms associated with disease, and also to control risk factors in order to reduce the risk of future problems. Some genetic changes may be associated with an increased risk of future problems, for example the presence of *PRSS1* mutations causing hereditary pancreatitis increases risk of pancreatic cancer by 50-70% (450). Research has shown that patients value information from predictive tests for medical and nonmedical decision-making and if information can be used to alter behaviour and the value of knowing encompasses other values, such as the value for the option to treat in the future if and when health technologies are available (499, 500). Chronic pancreatitis is an incurable chronic disease, and patients included in the study were made explicitly aware that, due to a pre-existing disease diagnosis, the findings of the genetic analysis would not be curative, or in fact significantly alter the clinical management. Instead, genetic testing offers patients the possibility of identifying the susceptibility to or contributes to aetiology of disease. Further to this, research also creates new means for disease prevention and future investigation into targeted cure (501). In the future, health promotion and treatment of disease will increasingly be based on individual genetic make-up (501). Debates surrounding the ethical principles of genetic testing are ongoing in the literature and centre on the moral and ethical obligations of testing. The decision to inform or not of genetic make-up, depends on the moral theory used with utilitarian and libertarian theories encompassing divergent outcomes (502). The current study included genetic testing of mutations that confer increased risk of disease development, and results do not mean that a disease will occur or remain absent. Inclusion in the study was entirely voluntary and the decision was

personal to each individual patient. Patients with chronic pancreatitis are subject to complex disease with variable aetiology, multifactorial aetiology, caused by several gene-gene, monogenic gene, and gene-environment interactions (473, 498). Susceptibility testing offers opportunity for patient education, counselling, knowledge of carrier status, potential for increased monitoring, and possible future treatment (501)

There are several important reasons why the analyses of genetic mutations are important to the thorough patient-centred evaluation of chronic pancreatitis;

- The identification of mutations in genes associated with pancreatitis can provide patients and clinicians with important information regarding a patient's individual risk for disease development
- The identification of the presence of mutations might result in earlier disease diagnosis, which in turn can facilitate earlier targeted aetiological-based treatment
- Outlining the potential contribution of genetic mutations can lead to the accurate determination of disease aetiology. This in turn can facilitate the development of genetic aetiology-based classification systems
- Knowledge of the mechanistic and functional consequences of gene mutations can allow for the development of targeted treatment
- Describing the pathogenesis of genetic mutations in associated disease, can further help to elucidate the clinical course of gene-associated syndromes and prognosis of disease
- The identification of mutations can allow for the evaluation of environmental factors and their implications on the phenotype and clinical course of genetic disease

- The identification of mutations may provide patients with answers as to why they, and not others, have developed the disease. This is particularly important in those categorised as having an alcohol aetiology, many of whom have rates of alcohol consumption which are significantly lower than levels required to produce harm

8.4.6. Future directions

The value of studies on genetic variations including covariates such as environmental factors, have led to a transformation in understanding of the pathogenesis of chronic pancreatitis. Chronic pancreatitis is a complex chronic disease confounded by genetic susceptibility and environmental factors, which increase sensitivity of the pancreas to stimuli that cause harm. Therefore due to the complexity, treatment requires a combination of aetiologically-tailored therapeutic interventions. In the near future patients with early signs of pancreatic disease will undergo genetic testing as part of comprehensive work-up and information derived will be used to treat specific aetiological factors. The contribution of genetic variants and other aetiological mechanisms have accentuated the important need for a personalised approach to patient care in those affected by chronic pancreatitis (503).

A challenging aspect of genetic association studies is determining the effect of candidate gene variants by statistical tests when the variant is rare or the effect of the mutation is uncertain. Despite this the association of rare variants and their contribution to disease phenotype and pathogenesis are important. Following on from this study, a full-*CFTR* gene sequence of patients with idiopathic and alcohol-induced patients is planned, to identify the presence of *CFTR* variants by examining the entire coding sequence. It is hoped that continued research into the phenotype-genotype correlations

of pancreas-associated genes will lead to therapies aimed at improving disease outcomes.

8.5. Strengths and limitations

8.5.1. Study strengths

The primary strength of the current study is the use of well-phenotyped idiopathic and alcohol-associated patients, and the fact that risk factors for the development of chronic pancreatitis were defined. The variants chosen for the mutational screening panel were chosen according to known published reports, and therefore genetic variants which have unknown clinical significance were excluded. The implications of this study are that it puts into perspective the types of chronic pancreatitis which are prevalent in Ireland. The data outlined in the current study are relevant and generalisable to other similar ethnic populations. The identification of genetic predisposition, particularly at early stages is important, and may help to expedite the diagnosis of chronic pancreatitis, and targeted therapies may be instituted.

8.5.2. Study limitations

As with all studies there are certain limitations which much be highlighted. This study used commercially available genetic testing which only evaluated selected variants on the three genes of interest and therefore, pathogenic negative patients may harbour gene variants which are not assessed using this method and therefore not evaluated in this study. Due to the non-validation of the *PRSS1* variant kits (no controls tested positive), patients have been informed that for clinical application and completeness the *PRSS1* variants will be re-examined. Further to this, it is likely that there are other

genetic or environmental factors which alone, or in combination, result in or influence the development of chronic pancreatitis (474). There were more females in the control group and the control group were younger than the patient group, which implicates comparison and this must be taken into consideration when interpreting the results. Analysis of the role of *CFTR* in idiopathic and alcohol induced chronic pancreatitis generally uses commercially available screening panels of common cystic fibrosis causing (rather than pancreatitis-causing) and pancreatitis causing mutations. Whether or not the chosen screening panels happen to include the relevant mutations for other disorders such as pancreatitis is unclear. In addition unusual mutations detectable exclusively by sequencing analysis might be present or absent in pancreatitis patients and therefore would not have been identified.

8.6. Conclusion

Pancreatic diseases appear to be heterogeneous disorders. Chronic pancreatitis is clearly a complex genetic disorder, with multiple associated signs and symptoms rather than an isolated disease. Multiple causative pathways converge into similar phenotypic features, and therefore a personalised approach to diagnosis and management is required. To better understand the role of trigger factors an accurate classification of the disease is required to better define which patient carry genetic susceptibility in association with morphological conditions and exogenous factors are at risk of developing acute, recurrent and chronic pancreatitis. Significantly, higher pathogenic variants were found in patients with chronic pancreatitis than controls and the overall diagnostic yield support the testing of patients. These observations are in accordance with current theories of complex disease genetics that many, perhaps several factors of relatively small effect, combine to produce a disease genotype. Regulatory variants

play a large role in complex diseases and these data support genetic testing in patients with idiopathic and alcohol-induced chronic pancreatitis.

9. Chapter 9 – Discussion

9.1. Summary of thesis objectives and findings

The overarching aim of this thesis was to investigate the management of chronic pancreatitis in Ireland. The objectives of this thesis were to examine the epidemiology, practice and factors relating to the clinical management of chronic pancreatitis. To achieve the objectives of this thesis, 4 inter-related studies were designed and conducted, and the study findings are summarised as follows:

1. Two nationwide surveys of the management of chronic pancreatitis in primary and secondary care in Ireland were first conducted to ascertain the current status on the management in Ireland. Results from these studies highlighted deficits in management in both healthcare settings, including lack of specialist services for patients, and lack of guideline knowledge. The studies specifically demonstrated that chronic pancreatitis is not currently managed as a chronic disease in primary care. The GP survey also identified a lack of guideline knowledge amongst specialists and a deficiency in guideline for primary care physicians. No provisions having been made in available consensus guideline for community level chronic pancreatitis management. Lack of guideline informing care for GPs was highlighted as an important barrier to good chronic disease management in primary care.
2. Results of the first study led to the design and dissemination of QRG guidelines for the primary care management of chronic pancreatitis, which was a direct outcome from results of the two nationwide surveys of practice.
3. The population based prevalence of chronic pancreatitis has not previously been quantified in Ireland. An epidemiological study of hospital activity revealed that the prevalence of chronic pancreatitis in Ireland was 11.6-13.4 per 100,000 of population. Double the amount of non-alcohol associated chronic pancreatitis cases were found in the study, which is of interest in a country with known, but

declining heavy alcohol use. A subsequent systematic review of published literature found that this result is in-line with some studies worldwide, which used counts of patients rather than estimations of caseload. There was increased chronic pancreatitis discharge activity in certain parts of Ireland, which could not be easily explained by alcohol consumption rates, deprivation data, cystic fibrosis prevalence or regional GP access.

4. Malnutrition remains a problem area in chronic pancreatitis management. Whilst knowledge in certain areas has evolved considerably, little attention has been focused on SIBO as a factor affecting malnutrition in chronic pancreatitis patients. To evaluate the prevalence of SIBO amongst non-surgical chronic pancreatitis patients with moderate and severe PEI, a cohort of 35 patients and 31 age-, gender- and smoking-status matched controls were recruited. The prevalence of SIBO in chronic pancreatitis patients was 15%, and no controls tested positive. This finding is in-line with the international pooled prevalence of SIBO in this cohort; however, it is clear that there is heterogeneity with regards to methods, protocols, and patient preparation in many of the reported studies. Notwithstanding this assertion, the results of the current study are comparable with a small number of studies which used similar methodology, excluding surgical patients, and using the recommended substrate. An association was found amongst patients with SIBO and diabetes, PPI use, PERT use and severity of PEI. Importantly, symptom improvement was reported in all patients following treatment with antibiotic. These findings, though in small numbers of patients, have important clinical implications for the management of chronic pancreatitis-related malnutrition.
5. The genetic study evaluated for the first time in and Irish cohort of chronic pancreatitis patients, pancreatic gene mutation variants, which are known to cause or to increase patient's susceptibility to the development of chronic pancreatitis. This study revealed that pancreatitis susceptibility or disease

modifying gene mutations are present in almost 18% of idiopathic and alcohol-induced chronic pancreatitis patients. The presence of these mutations increases patients risk of disease by almost four-fold when compared to the general population. The disease modifying gene mutation *SPINK1* N34S was particularly enriched in patients when compared to controls and the presence of this mutation increased the risk of disease in patients almost 5-fold.

9.2. Novel and original contributions to knowledge

9.2.1. Management & guidelines

The two nationwide surveys of practice represented the first studies of their kind in Ireland and among the first in Europe, providing valuable insights into the current management of patients with chronic pancreatitis from two important healthcare settings, where the majority of care takes place. For the first time, deficiencies in practice in comparison to recommended guidelines were reported, identifying an opportunity for education and training. Specific areas for improvement were identified including; communication between primary and secondary care, access to specialist services and nutritional management of chronic pancreatitis. Lack of guideline awareness amongst specialists was identified, but importantly a deficiency in the existence of guideline for GPs was identified. This research provides a measure of chronic pancreatitis disease management in Ireland and places Ireland within an international context with regard to a benchmark of chronic care.

Directly as a result of the findings from the GP survey, came the development of QRG guidelines for the primary care management of chronic pancreatitis in collaboration with the ICGP, which are the first of their kind in Ireland and among the first in Europe. The provision of guidelines for GPs that were previously not available will ensure that care is research driven, safeguarding the best patient outcomes.

9.2.2. Epidemiology

The findings of the first surveys of practice led the author to the design of the second study aimed at quantifying the population based burden of the chronic pancreatitis in Ireland. A retrospective hospital based analysis of in-patient discharges showed a hospital-discharge prevalence which is consistent with reports from studies worldwide. An unexpected finding was that there were double as many hospital discharges for patients with non-alcohol related chronic pancreatitis which has implications for clinical practice, in consideration of other causes of chronic pancreatitis, and with regard to accurate aetiological classification.

Subsequent to this study, a systematic review of available epidemiological studies was conducted, to help situate Ireland within the context of worldwide epidemiological reports. This review indicated that the differences in prevalence and incidence rates reported worldwide may be attributable to differences in diagnostic criteria, differences in data collection methodology and studies being conducted at different time points. Studies using counts of patients, including patient-specific clinical data are arguably more accurate for estimating population-based disease burden.

9.2.3. Intestinal microbiota / SIBO

The finding of SIBO in 15% of non-surgical chronic pancreatitis with moderate to severe PEI is clinically important. Many patients with PEI and chronic pancreatitis suffer with ongoing malabsorbtive symptoms which often are uncontrolled despite adequately prescribed PERT regimens. In some cases, intractable symptoms exist, and other potential causes of malabsorption in chronic pancreatitis patients should be considered. The symptoms of SIBO are non-specific, and there is an overlap with the symptoms of PEI in chronic pancreatitis, meaning a high degree of clinical suspicion is necessary to diagnose patients. SIBO is easy to detect in clinical practice, and GHBT is

a widely available, efficient, and cost effective method of diagnosis. The current study demonstrated symptom improvement post antibiotic treatment in all SIBO positive patients. This finding is important in clinical practice, and the adoption of SIBO analysis into clinical work-up for symptomatic patients deserves consideration.

9.2.4. Genetics

The genetic study highlighted the presence of gene mutations in almost 18% of idiopathic and alcohol-associated chronic pancreatitis patients which was significant. Variants in *SPINK1* were particularly prevalent amongst patients, and the presence of this gene is mutation, known to modify chronic pancreatitis, particularly in the context of environmental toxins is important. Chronic pancreatitis is a complex, highly unpredictable genetic disease, consisting of signs and symptoms which differ between patients of similar aetiology. Analysis of the comprehensive range of susceptibility variants can support the modelling of the effects of genes and environment in individual patients with pancreatitis. Genetic analysis of individual patient risk is useful clinically and provides clinicians an opportunity for early intervention. This also has important implications for individual patients, especially in patients deemed to be abusing alcohol. There is need for ongoing discussion and revision of existing protocols to include genetic screening in patients with unclear aetiology, and a suspected genetic basis to their disease.

9.3. Implications for clinical practice

Results of the studies undertaken to fulfil the aims of this thesis have a number of important implications for clinical practice which are discussed below.

9.3.1. Management of chronic pancreatitis

The data gleaned from the two surveys of chronic pancreatitis in Ireland have important implications for clinical practice. There is a need to build upon epidemiological data and use results to guide service development in a meaningful and effective way, especially in the healthcare system situation where demand will consistently surpass resources. This baseline measure may be used to determine future changes to augment the management of chronic pancreatitis. It is clear that improvements to chronic disease management in both secondary and primary care are required. The poor response rate from the specialist group limits applicability of findings, and potential reasons have been outlined in Chapter 5. However, some important facets were extracted which implicate clinical practice. Investments in services which are fundamental to chronic pancreatitis are required in secondary care to improve clinical management. The absence of dietitian and multidisciplinary teams are actionable and should be addressed to ensure patients are receiving appropriate chronic disease care. Results from the management of chronic pancreatitis in hospital-based care emphasised that the availability of clinical guidelines does not assure implementation or compliance, and the lack of guideline awareness amongst the group was apparent. Educational opportunities and dissemination strategies must be created to increase guideline-uptake and implementation. Well thought-out education strategies and dissemination opportunities for guidelines are necessary. This may include presentation at local or international conference as well as inclusion of pertinent studies and reviews in international consensus guidelines.

These results support the need to develop and integrate shared care of patients with chronic pancreatitis between secondary and primary care. There is an element of inequity in access to services in some healthcare settings, which can impact patient care. The survey revealed that some specialists provide care for chronic pancreatitis

patients in isolation, and without the use of recommended guidelines, and sometimes without essential multidisciplinary support. A national chronic pancreatitis disease programme is required, to improve and reform the quality of care, improve access to services, whilst ensuring a sustainable programme. A national chronic pancreatitis programme could enable the provision of integrated care across the healthcare system. This can be accomplished by the disease specific national clinical directorate, responsible for defining health service delivery for chronic diseases by the Health Service Executive (162).

Primary care physicians play an active role in the management of chronic pancreatitis. Irish GPs have self-reported significant chronic pancreatitis-specific knowledge deficits. Primary care services experience significant communication barriers when attempting to access specialist pancreatic team advice and information. The roles and responsibilities specific to chronic pancreatitis management in primary care are undefined, inconsistent, unstructured and geographically unequal. The primary care setting would benefit from adequately resourcing and funding chronic disease management to improve patient care. To address some aspects of the issues identified, primary care guidelines for the management of chronic pancreatitis have been created and published, accessible to all GPs nationwide (124). This included a visual aid in the form of a flow-diagram which can assist GPs with decisions regarding chronic pancreatitis management. These guidelines also contain contacts for specialist services and GPs may refer patients of concern to specialist centred for chronic pancreatitis management. The complexity and increasing prevalence of chronic disease has placed considerable significant responsibility on the overburdened and under resourced primary care sector. Whilst health policy has targeted certain diseases (diabetes, hypertension) there is need to highlight other conditions in which significant deficits exist in service provision and patient outcomes. One actionable outcome from this study has already been fulfilled, in the provision of primary care guidelines for

chronic pancreatitis management. However, there is need for a primary care strategy specific to chronic diseases such as chronic pancreatitis which would be implemented within the general framework of chronic disease management. Such a strategy must be incorporated with a focus on shared care of patients between primary and secondary care. These actionable aspects of chronic pancreatitis management which have implications for clinical practice may be accomplished through restructuring, resourcing and funding primary care in Ireland.

9.3.2. Epidemiology

Measurement of incidence, prevalence and hospital utilisation is central to chronic disease management programmes and results are applicable in clinical practice. Providing trends in disease and risk factors can reduce uncertainty in medical and nursing reasoning, especially in the case of unclear signs, variable test data and confusing treatment results (504). The analysis of case clustering and hospital utilisation of chronic pancreatitis over time allows knowledge of disease aetiology in Ireland. The finding of double the amount of non-alcohol associated disease aetiology is an important consideration in clinical practice, and may allow for more consideration of the value genetic testing. Descriptive epidemiological data is important to delineate the probability of a specific disease in contrast to other clinically similar entities.

Results are also applicable to a wider audience of healthcare policymakers, strategists and budget allocators. Knowledge of the frequency of disease allows for planning of strategies to decrease disease occurrence, and to reduce consequences of disease for patients and society. Furthermore the results from the systematic review on the epidemiology of chronic pancreatitis in Chapter 7 revealed increasing rates in prevalence, incidence and hospitalisation in other jurisdictions. This evidences the need for health strategies aimed at reducing modifiable disease risk factors such as alcohol, smoking and diet.

9.3.3. Small intestinal bacterial overgrowth

The evaluation of SIBO presence, eradication with antibiotic therapy, and reported symptom improvement are important to consider in improving patient care. The significance of SIBO in chronic pancreatitis has been researched, but is especially important in conjunction with moderate PEI as the symptoms of both overlap. Improvements in patient care may result from introducing SIBO testing into routine clinical practice and work-up for patients with intractable malabsorptive symptoms. Breath testing is inexpensive, efficient and non-invasive and can be clinically useful to detect SIBO. In the absence of gold standard, adopting the recommended guidelines for use including with strict patient preparation may be useful in clinical practice. Care should be orientated to finding the best method to reduce patient symptoms. A test, treat and evaluate system may be valuable in clinical practice.

9.3.4. Genetics of chronic pancreatitis

In patients with early signs of pancreatic disease, systematic evaluation, including genetic analysis may increase the occurrence of early aetiology-based diagnosis. This in turn can provide targeted aetiology-based treatment and modification of risk factors, which may help to reduce or slow disease progression. Knowledge of genetic risk factors is important for counselling patients. This is especially true in the context of modifiable risk factors, it is important for clinicians to have research evidence of genetic risk in order to appropriately counsel patients. This may in part improve disease outcomes and allow patients involvement in treatment. It is unclear in clinical practice which patients should receive genetic testing, and knowledge of the prevalence of genetic risk factors can help to inform diagnostic guidelines. Epidemiological

knowledge of non-modifiable risk factors, such as genetic predisposition is also important as it influences disease occurrence, and therefore requires services to be planned accordingly.

9.4. Implications for policy

Results of the studies undertaken to fulfil the thesis aims have a number of important implications for policy. Chronic pancreatitis is a chronic incurable disease which has a multitude of healthcare and socioeconomic requirements for patients, and for the broader healthcare system. Chronic diseases contribute to decreased quality of life, increased morbidity, higher mortality, and their prevention, treatment and management constitute a considerable proportion of healthcare resourcing and expenditure in Ireland and worldwide (3, 148). The studies undertaken in the current thesis highlight noteworthy deficits and barriers to the management of chronic pancreatitis in primary and secondary care in Ireland. These findings point towards substantial inefficiencies and inadequacies to comprehensive and equitable chronic disease management. Designing, developing and implementing integrated and sustainable health and social care services for future Irish healthcare is essential.

Chronic disease management programmes and initiatives should be patient centred, operating within the overall requirements of the Department of Health framework on chronic disease management (3) and align with the Sláintecare vision for new healthcare service in Ireland (316). The National Clinical Programme is providing the foundations for patient-centred and coordinated Integrated Care Programmes in Ireland. A National Model of Care for chronic pancreatitis management is required by all healthcare professionals involved in the management of patients, to change and improve the delivery of chronic pancreatitis management. The Integrated Care model

should be designed with tri-involvement from primary, secondary and tertiary care service. This should incorporate a number of important considerations and facets in disease prevention and management and ensuring a high-quality, accessible and cost-effective service for all patients. This must be a flexible, adaptive, interdisciplinary and consistent with patients' needs as developments occur during the course of disease. Under the shared care model, patients should receive high quality care through a management plan, appropriate to their needs, including equitable access to services, throughout the course of illness (3). Further to this, there is need for the Department of Health and relevant bodies to continue to develop disease-specific self-care programmes for patients with chronic conditions.

As outlined in Healthy Ireland (156) a whole government approach, including intersectoral action and structures are essential to create environments that support and promote health, build public health policy, and reduce the burden of chronic diseases. Chronic diseases such as chronic pancreatitis are also relevant in the context of development of new contracts, specifically relating to the GMS contract. This is also relevant to consultant contracts where the development of shared care models and integrated services is an important requirement (3).

9.5. Suggestions for future research

9.5.1. Future directions

The work described herein has developed from previous core research from the pancreatic diseases and nutrition collaborative multidisciplinary research group in; The Trinity Centre for Health Sciences at Tallaght Hospital, The Centre for Pancreatico-Biliary Diseases in Tallaght Hospital, The Hepato-Biliary Surgical Service at St Vincent's University Hospital, Dublin, and the Department of Surgery, Trinity College Dublin. This collaborative core group are supported by several disciplines and

departments in Tallaght Hospital and St Vincent's University Hospital (including the Departments of Biochemistry, Endocrinology, Clinical Nutrition and Dietetics, Gastroenterology, Radiology and Nursing). Building on findings from this thesis, several have been designed and have commenced or are due to commence in the coming months;

1. Results of the epidemiological study of chronic pancreatitis hospital activity in Ireland revealed that there is significant hospital-related activity for the disease treatment. Therefore, an investigation of the financial burden of chronic pancreatitis for the Irish healthcare system is warranted
2. Following from the survey of GPs and the need for increased education on chronic pancreatitis management, the development of an online continuing medical education module for the primary care management of chronic pancreatitis is proposed. It is hoped that this will have an interdisciplinary focus and target multiple stakeholders to improve knowledge in patient management
3. Results from the SIBO study indicated that patients who tested positive and were treated with antibiotics reported symptom improvement post treatment, and this finding has been corroborated in other gastrointestinal disease. The next step is to evaluate the effect of antibiotics in symptom eradication in patients with SIBO and chronic pancreatitis as this is identified as an area which is lacking knowledge
4. Chronic pancreatitis disease related mutations were found to be present in 20% of the idiopathic and alcohol-related patients who were tested. This study examined the presence of only a small number of selected variants. Whole exome sequencing of major pancreatic gene mutations in chronic pancreatitis patients is planned in collaboration with Genomics Medicine Ireland, to identify DNA variants which are predicated to increase the risk of pancreatitis

Together with the body of research which has been published to date, this thesis, and research studies strive to improve the management of patients with chronic pancreatitis.

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Appendix A. Sample conference posters

The prevalence of chronic pancreatitis does not appear to be due to alcohol usage in Ireland

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Introduction

There are no data regarding the prevalence, hospitalisation, or aetiology of chronic pancreatitis (CP) in Ireland. Comprehensive study of CP is required to plan services, inform guidelines and facilitate a rational allocation of services. Prior work from our unit showed an increase in alcohol-related admissions for acute pancreatitis in Ireland[3]. It is unclear if this has caused an increase in CP admissions.

Aims

We sought to analyse patient discharge activity for CP in Ireland, to investigate temporal data, trends in age, gender, aetiology, admission type, diagnoses, procedures , discharge status, and geographical and socioeconomic variation and to estimate a national CP prevalence. A secondary aim was to conduct a systematic review of international CP prevalence studies

Methods

A nationwide retrospective study of in-patient discharges from acute public hospitals participating in Hospital In-Patient Enquiry (HIPE) database. We searched for ICD codes K86.0 alcohol-induced CP and K86.1 Other CP from 2009-2013. A systematic literature search was undertaken to identify studies reporting on prevalence, incidence and hospitalisation.

Continent	Author, publication year	Country (region where applicable)	Year(s) studied	Study type	Patient type	Prevalence	Incidence	Hospitalisation
Europe	**Ní Chonchubhair (Current study)**	**Ireland**	**2009-2013**	**Hospital in-patient enquiry (national hospital discharges)**	**CP**	**11.6-13.4 per 100,000**		
	Dzieniszewski & Jarosz, 1990	Poland (Warsaw)	1982-1987	Hospital survey	CP	17.0 per 100,000	5.0 / 100,000	-
	Jaakola & Nordback, 1993	Finland	1970-1980	Hospital discharges			13.4 per 100,000	
	Lévy, 2006	France	2006	Survey of gastroenterologists	CP	26.4 per 100,000	7.7	-
	Dite, 2001	Czech Republic	1999				7.9 per 100,000	
	Dominguez-Munoz, 2014	Spain	2014	Survey of specialists	CP	49.3 per 105,000		-
	Joergensen, 2009	Denmark	1980-2004	Registry	CP	11.7 – 17.0 per 100,000		-
	Andersen, 1982	Denmark	1970-75 1975-79	Retrospective study	ACP		6.9-10.0 per 100,000	
	Lankisch, 2002	Germany	1988-1995	Patient records	CP		6.4 per 100,000	
	Tinto, 2002	England	1989/90 – 1999/2000	Hospital episode statistics	CP	-		4.3 (1989/1990) to 8.6 (1999/2000) per 100,000 (100% increase for CP)
	Spanier, 2008	Netherlands	1992-2004	National database	CP	-		Admission rate 8.5 per 100,000 (75.4% increase)
	Spanier, 2013	Netherlands	2000-2005	Registry / linked cohort	CP		1.8	
	Johnson & Hosking, 1991	United Kingdom	1960-1984	Hospital discharge records			4.3 (male) 2.1 (female) / 100,000	
United States	Yadav, 2011	USA (Olmsted Co)	2011	Chart review	CP	41.8 per 100,000	4 per 100,00	-
	O'Sullivan, 1972	USA (Rochester)	1940-1969	Patient records			8.7-14.9 per 100,000	
	Yadav, 2011	USA (Pennsylvania)	1996-2005	Healthcare cost dataset	CP	-		Rate: 7.75 per 100,000
	Yadav, 2007	USA	2002-2003	Chart review and medical diagnostic index	CP and AP	3% (of 1409)		-
	Garg, 2015 (conference abstract)	USA	1997-2012	National database	CP	-		Admissions decreased from 8 to 4.5 per 100,000
	Shastri, 2014 (conference abstract)	USA	2002-2010	National database	CP	-		Admissions decreased from 24,701 to 19,809
Asia	Wang, 2009	China	1996-2003	Survey	CP	3.08 to 13.52 per 100,000		-
	Lin, 2000	Japan	1994	Survey	CP	28.5 per 100,000	5.4 / 100,000	
	Otsuki, 2005	Japan	2002	Survey	CP	35.5 per 100,000	14.4 / 100,000	
	Hirota, 2012	Japan	2007	Large-scale nationwide survey	CP	36.9 per 100,000	11.9 / 100,000	
	Hirota, 2014	Japan	2011	Large-scale nationwide survey	CP	52.4 per 100,000	14.0 / 100,000	-
	Tandon & Garg, 2004	Asia – Pacific	2004	Survey	CP	4.2–114/200 per 100,000		-

Table 1. Worldwide studies on prevalence, incidence or hospitalisation for chronic pancreatitis
ACP Autoimmune Pancreatitis, CP chronic pancreatitis, AP acute pancreatitis

Results

- Irish CP prevalence was 11.6-13.0 per 100,000
- 'Other' aetiology CP discharges were double that of 'alcohol-induced' CP
- Males >65% patient activity each year
- Majority of discharges were in the 40-64yr age group
- Most CP admissions were 'emergency non-readmission' accounting for 66.5%-72.1% of all episodes
- Notable geographical variation in CP patient discharge activity, higher activity in the Northwest
- Table 1 details the results of the systematic literature search

Conclusions

- Our prevalence is similar to worldwide studies who adopted a similar methodology using exact counts of patients (rather than surveys)
- Prevalence is undoubtedly underestimated as it is based on in-patient discharges only excluding primary care, outpatient and emergency room visits without admission
- Regional variations in CP activity could not be easily explained by geographical differences in alcohol consumption, cystic fibrosis prevalence, social deprivation or general practitioner access
- These results represent valuable prevalence and hospital activity data for a disease about which relatively little is known

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Supported in part by an unrestricted educational grant from Mylan

Small intestinal bacterial overgrowth in chronic pancreatitis patient with pancreatic exocrine insufficiency; a prospective cohort study

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Introduction

Small intestinal bacterial overgrowth (SIBO) can result from failure of the gastric acid barrier, failure of small intestinal motility, anatomic alterations or impairment of systemic and local immunity. Clinical manifestations of SIBO are variable and include bloating, flatulence, abdominal pain, abdominal distention and diarrhoea. Most patients with CP experience similar symptoms, which are usually related to pancreatic exocrine insufficiency (PEI). PEI also causes malabsorption and is a major complication of chronic pancreatitis (CP) and could worsen symptoms and nutritional status. The therapeutic options for the medical treatment of CP include the administration of pancreatic enzyme replacement therapy (PERT) which reduces these symptoms. When symptoms are not relieved by PERT, other causes should be evaluated, including SIBO. A recent systematic review[3] reported the occurrence of SIBO in 3-92% of patients with CP

Aims

- We sought to determine SIBO prevalence in idiopathic and alcohol aetiology CP patients with PEI (Faecal Elastase-1 <200ug/g) *versus* matched healthy controls

Methods

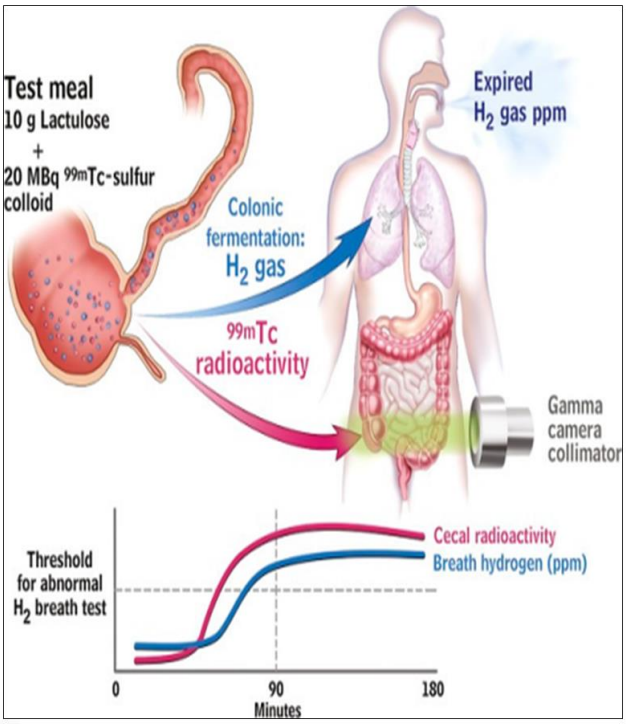
- Thirty-three patients with CP and 18 controls (matched for age, gender and smoking status) underwent glucose hydrogen breath-testing (GHBT), using glucose substrate
- Patients were asked to fast for a minimum of 12 hours prior to breath-testing
- Patients were excluded if they had undergone previous gastric / pancreatic / intestinal surgery or if they had any malignancy
- Patients were excluded if they had antibiotic treatment <4 weeks prior to study
- Patients were asked to refrain from smoking while fasting for the study (minimum 12 hours)

Results

- The majority of patients (67%) were male with a mean age of 52.4years
- More patients (48.5%) than controls (27.8%) were smokers, but this was not statistically significant (P=0.151)
- SIBO was positive in 4/33 patients (12.2%) while no controls were positive
- There was no association found between the presence of SIBO and gender (P=0.283), diabetes (P=0.120), PPI use (P=0.289) and pancreatic enzyme replacement therapy (PERT) (P=0.124)

Discussion

- This represents the first Irish data for the prevalence of SIBO in CP patients
- The reported prevalence of SIBO amongst CP patients is wide ranging, from 3-92%[3]
- At 12.2% prevalence, SIBO in this group of alcohol / idiopathic CP patients is similar to other studies utilising GHBT
- This low prevalence might be attributable to the use of the recommended substrate glucose, rather than lactulose which is known to result in more frequent positive results
- Low prevalence might also be attributable to the exclusion of patients with a surgical history, also increasing SIBO positivity
- Nevertheless, we recommend that patients with CP who are unresponsive to high-dose PERT should be tested for the presence of SIBO



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Centre for Pancreatico-Biliary Disease

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The First Report of Chronic Pancreatitis Prevalence and Hospital Activity in Ireland

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Introduction

Chronic Pancreatitis (CP) is an irreversible, inflammatory and fibrotic disease of the pancreas which is characterised by progressive impairment of pancreatic exocrine / endocrine function and chronic pain. The predominant aetiology worldwide, and particularly in western countries is alcohol. In Ireland, little is known about the management of CP and there are no epidemiologic data to inform health strategies. The reported European prevalence ranges from 12-50 per 100,000 population

Aims

- We sought to establish the prevalence of CP in Ireland
- We also aimed to examine age/gender/geographical trends in patient activity over 5 years

Methods

- Using the Hospital In-Patient Enquiry (HIPE) database, we retrospectively reviewed discharge information for CP patients from 2009-2013
- Chronic Pancreatitis & Alcohol-Induced Chronic Pancreatitis ICD-10 Codes K86.0 & K86.1 were searched
- The following data were obtained: 'total unique patients', 'total patient discharges', 'total patient discharges excluding day-case', 'total bed days', 'mean/median bed days', 'intensive care unit (ICU) days'
- 'Total patient discharges' includes hospital discharges in any given year and therefore patients are counted for every inpatient stay
- 'Total unique patient' - only counts each patient once, referring exclusively to one patient discharged from a hospital with CP in any given year
- Age & gender breakdown were obtained for total unique patients and total patient discharges separately
- To calculate prevalence, 'total unique patients' was used as a numerator and the total resident population as a denominator
- National Census Data 2011 (Central Statistic Office) was used to calculate total resident population

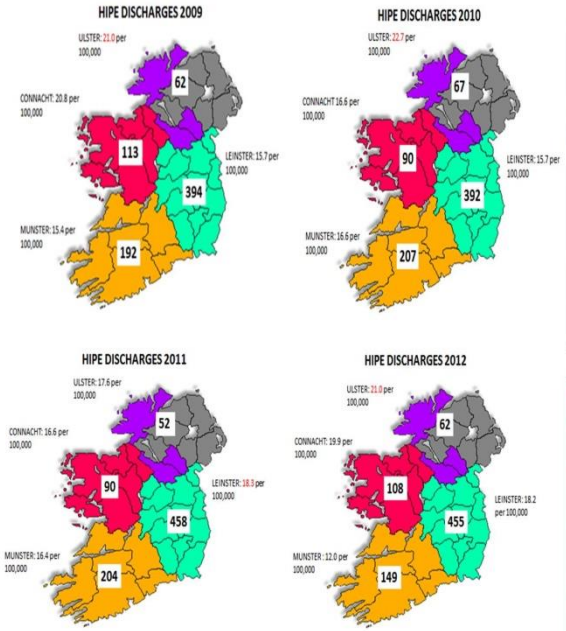

Figure 1: Prevalence per county capita and province 2009-2012

- ✓ **Regional Variation**
- ✓ **High prevalence pockets in the Northwest**
- ✓ **High volume centres – Dublin & Donegal**
- ✓ **Majority male, 30-69 years**
- ✓ **CP patients occupied on average 17.2-22.8 beds per year**

Results

- The prevalence of CP in Ireland ranged from 11.7 to 13.7 per 100,000 population between 2009-2013, and appeared to stay level during this period
- The majority were male (55-71.2% between 2009-2013), and most were 40-69years.
- There was geographical variation; the Northwest had the highest patient activity (patient discharges) per capita (17.6-22.7 per 100,000) over 5 years
- Total bed days ranges from 6,613 to 7,224 annually corresponding to 18.8-20.9 full-time CP-occupied beds in Ireland from 2009-2013

Discussion

- This represents the first epidemiologic data for CP prevalence in Ireland
- Prevalence appears to be significant, with regional variations requiring further investigation
- Prevalence rates are undoubtedly **underestimated** as data only accounts for patients hospitalised in any given year
- The resource burden of CP is emphasised by the constant use of 19-21 in-patient beds throughout the study period
- Phase 2 is a more targeted and in-depth study will look at HIPE CP data over 20 years for disease aetiology, patient age, gender, LOS, smoking, alcohol use and cost of care to provide data and profile patients with chronic pancreatitis in Ireland

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Chronic Pancreatitis in Primary Care – The Management of an Orphan Disease

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Introduction

Chronic Pancreatitis (CP) is an irreversible, inflammatory and fibrotic disease of the pancreas which is characterised by progressive impairment of pancreatic exocrine / endocrine function and chronic pain. There are no data regarding the incidence, prevalence, hospitalisation, aetiology or management in Ireland, nor have the experiences / insights of front line clinicians been sought

Background & Aims

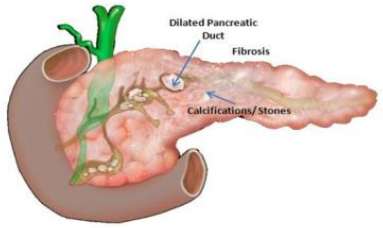
We devised a survey for use with general practitioners to determine national and regional trends in CP management in the Primary Care setting, and to obtain their insights, experiences, and concerns in the management of CP and the proposed development of a national CP disease registry

Methods

A 23-question survey was twice posted to 563 randomly selected GPs (list derived from the Irish National Cervical Check Directory). The survey was first subject to pilot (n=20) for usability and purpose

Results

- 389 surveys were completed, yielding a 69% response rate
- Most respondents (62%) were male and 88% had >8years GP experience
- 96% had no knowledge of any national or international consensus guidelines for CP management
- Whilst 57% of GPs reported having between 1-3 CP patients currently in their care, 30% actually code for these in their practice
- Almost half (43%) have no access to a specialist multidisciplinary team support
- 49% indicated a CP disease registry would be a useful undertaking, however only 28% felt it would be actively used and 56% were unsure of its use
- Only 27% were happy to provide ongoing care for these patients
- Suggested improvements included primary care management guidelines, education, access to specialist care, access to MDT and dietitian
- GPs listed barriers to good care that CP patients experience in primary care, and these included lack of time, no community resources, lack of knowledge, no support services and no access to specialist services



Conclusions

- ✓ Deficits exist in guideline knowledge, MDT support and CP management in the Irish Primary care setting
- ✓ Limited MDT access and availability
- ✓ Most GPs were unhappy at the prospect of ongoing CP care
- ✓ Many GPs were unsure if a disease registry would be utilised by healthcare professionals
- ✓ No payment for chronic disease care
- ✓ Many suggested improvements and barriers to good patient care
- ✓ The survey was couched with reference to the principals of good chronic disease management, and based on these results, evidently CP is not currently being managed as a chronic disease

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Small intestinal bacterial overgrowth in chronic pancreatitis patient with pancreatic exocrine insufficiency: a prospective cohort study

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Introduction

Small intestinal bacterial overgrowth (SIBO) can result from failure of the gastric acid barrier, failure of small intestinal motility, anatomic alterations or impairment of systemic and local immunity. Symptoms of SIBO include bloating, flatulence, abdominal pain, abdominal distention and diarrhoea. Patients with CP may experience similar symptoms due to pancreatic exocrine insufficiency (PEI). PEI also causes malabsorption and is a major complication of chronic pancreatitis (CP) leading to adverse symptoms and poor nutritional status. The administration of pancreatic enzyme replacement therapy (PERT) to treat PEI is the mainstay of treatment. However when symptoms are not relieved by PERT, other causes should be evaluated, including SIBO. A recent systematic review[1] reported the occurrence of SIBO in 3-92% of patients with CP

Aims

- To determine SIBO prevalence in idiopathic /alcohol aetiology, non-surgical CP patients with PEI (faecal elastase-1 <200ug/g) *versus* matched healthy controls

Methods

- 34 patients and 26 controls (matched for age, gender and smoking status) underwent glucose hydrogen breath-testing (GHBT), using glucose substrate following a minimum 12 hour fast from food and smoking
- Exclusion criteria included history of gastric /pancreatic / intestinal surgery, any malignancy, or antibiotic treatment <4 weeks prior to study
- GHBT was performed using a breath analyser (LactoFAN H2, Medical Diagnostics, Australasia). Subjects were asked to avoid slowly released carbohydrates (bread/potato), fibre, and a heavy meal in the last meal before fasting. Strenuous exercise was avoided for <24 hours before testing. Following baseline breath sample, patients ingested 250ml glucose substrate and breath hydrogen values were estimated every 20 min for 180 min. A persistent rise in breath hydrogen levels 12ppm above basal levels was diagnostic of SIBO
- We conducted a systematic search of published studies examining the prevalence of SIBO in CP.

Results

- Patients and controls were closely matched (Table 1)
- SIBO was positive in 5/34 patients (14.7%) and no controls, however this was not statistically significant (*p*=0.063)
- There was no association between the presence of SIBO and gender (P=0.150), or PPI use (P=1.000), while PERT was just outside of significance (P=0.052)
- Among patients, those with diabetes were more likely to have SIBO (P=0.031)
- 9 studies were retrieved (prevalence of SIBO 0-92%). Three studies used LHBT, 4 studies included only alcohol-related patients. Three studies were uncontrolled, 3 studies recuited post-surgery CP patients, and 2 studies did not report if their cohort was surgical. Two studies also employed controls who had received surgery. Only two studies (including the current study) showed any relationship between SIBO and any other factor.

Discussion

- This is the first Irish data investigating SIBO in CP patients
- We report a prevalence of SIBO in our non-surgical CP cohort of 14.7% and 0% of controls, which was similar to other studies with similar methodology (Including glucose substrate), but on the lower end of prevalence compared to other studies (Table 2). This may be due to the use of a glucose substrate (lactulose is known to result in more positive results, and is not recommended for the measurement of SIBO[2])
- The relatively low prevalence might also be due to the non-surgical CP group, as surgery is known to contribute to SIBO
- These findings would not mandate blanket testing, however we recommend that those with ongoing symptoms with apparently adequate dosage of PERT, and especially those with concurrent diabetes, could benefit from SIBO testing

	Cases (n=34)	Controls (n=26)	P-value
Sex (M:F)	23:11	15:11	0.433
Age,(SD)	52.3 (10.5)	53.3(10.5)	0.997
Smoker[n(%)]	47.1% (16)	34.6% (9)	0.307

Table 1. Demographic or patients compared to controls

Author (Year)	Test	Patients	Aetiology	Surgery	Controls	Control Characteristic	Result(P&C)	Relation
Madsen (2003)	GHBT	11	Alcohol	N/R	-	NA	0% & N/A	No
Kumar (2014)	GHBT	67	Alcohol/Idiopathic	N/R	74	Healthy	14.7% & 1.3%	Diabetes P=0.07
Signoretti (2014)	GHBT	43	Alcohol/Other	No	43	Unspecific / GI complaints	21% & 14%	No
Trespi (1999)	GHBT	35	Alcohol	Yes	61	Gastric resected,	34% & 21%	No
Lembcke (1985)	GHBT	20	Alcohol	No	-	-	40% & N/A	No
Casellas (1998)	GHBT	15	Alcohol	Yes	15	Immunodeficient, surgical	40% & 6.7%	No
Grigor'eva (2010)	LHBT	102	N/R	No	-	-	79% & N/A	No
Mancilla (2008)	LHBT	14	Alc/Idio/Auto	Yes	14	Healthy	92% & 14%	No
Current study (2017)	GHBT	34	Alcohol/Idiopathic	No	26	No surgery, healthy, matched	14.7% & 0%	Diabetes P=0.03

Table 2. Results from systematic search of published studies on SIBO prevalence in CP

References
1 Capurso, G. , Signoretti M., Archibugi L., Stigliano S., Delle Fave, G. Systematic review and meta-analysis: small intestinal bacterial overgrowth in chronic pancreatitis. United European Gastroenterology Journal. 2016, 1-9.
2 Gasbarrini, A., Corazza, GR., Gasbarrini, G. *et al.* 1st Rome H2 breath-testing consensus conference working group. Methodology and indications of H2 breath testing in gastrointestinal diseases: The Rome Consensus Conference. Aliment Pharmacol Ther 2009;29: 1-49
3 Saad, RJ ., Chey, WD. Breath testing for small intestinal bacterial overgrowth: maximising test accuracy. Clin Gastroenterol Hepatol 2014; 12: 1964-1972

Centre for Pancreatico-Biliary Disease

Sponsored in part by an unrestricted educational grant from Mylan

Appendix B. Letters of ethical approval / permission

St. Vincent's Healthcare GROUP LIMITED

UCD DUBLIN

Ethics and Medical Research Committee
ELM PARK, DUBLIN 4
Tel. (01) 2214117 Fax (01) 2214428
email: joan.mcdonnell@ucd.ie or jacinta.mcmanus@ucd.ie

2nd November, 2015.

Professor K. Conlon,
Professor of Surgery,
Department of Surgery,
St. Vincent's University Hospital,
Elm Park,
Dublin 4.

Re:- The epidemiological clinical and genetic aspects of chronic pancreatitis in Ireland. **Response Letter dated 27/10/15.** Protocol Summary. Application form August 12th 2015. Appendix 1 – **Letter for Participation revised 22/9/15.** Appendix 2 – Subject suitability screening form. Appendix 3 – Chronic Pancreatitis standing assessment form. Appendix 4 – Study Poster. Appendix 5 – Letter to GP. Appendix 6 – Chronic Pancreatitis pain scale. CFQR Cystic Fibrosis Questionnaire – Revised version 2. EORTC QLQ-C30 (version 3). SJH/AMNCH Ethics approval letter. APA Practice Guideline in Chronic Pancreatitis (Conwell et al, 2014). Study 1: An Investigation of genetic mutations in an Irish cohort of chronic pancreatitis patients. **PIL/Consent vs 1. Studies 2 & 3. 1) Microbiome analysis and 2) Small intestinal Bacterial Overgrowth (SIBO) in chronic Pancreatitis. PIL/Consent Revised version 22/9/15**

Dear Professor Conlon,

We have received the revised documents and clarification from Ms Hazel Ni Chonchubhair, the Ethics and Medical Research Committee meeting held on Wednesday 2nd September 2015 at which the above study was reviewed.

Following review of the revised documents and clarifications, this study is now granted full ethical approval.

Yours sincerely,

Dr. E. Molloy,
Chairman,
Ethics & Medical Research Committee

cc. Ms Hazel Ni Chonchubair, Dept of Surgery, Trinity Centre for Health Sciences.

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

Ms. Hazel Ni Chonchubhair
The University of Dublin, Trinity College
Tallaght Hospital
Department of Surgery
Room 1.29 Trinity Centre for Health Sciences
Tallaght
Dublin 24

29th June 2015

RE: The Epidemiological Clinical and Genetic Aspects of Chronic Pancreatitis in Ireland

REC Reference : 2015-03 List 11 (2) 2015 List 21 (7)
Please quote reference on all correspondence

Dear Ms. Ni Chonchubhair ,

Thank you for your correspondence dated 22nd June to SJH/AMNCH Research Ethics Committee requesting approval for an amendment to the above study.

The Chairman, on behalf of the Research Ethics Committee, has reviewed and approved your amended correspondence.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

Appendix C. General Practitioner survey letter

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Dear Colleague,

We are writing to you to request you to participate in a national survey of general practitioners and specialists which is being carried out by our research group at the Departments of Surgery and Public Health and Primary Care at Trinity College Dublin.

The purpose of this research is to better understand your experience as senior clinician, regarding chronic pancreatitis and its management in the primary care setting in Ireland. This survey will provide information and guidance for the future development of services for patients, will inform the development of a chronic pancreatitis disease registry and will inform the design of appropriate educational modules across disciplines. There is no data regarding incidence, prevalence, hospitalisation or aetiology of chronic pancreatitis in Ireland, nor has the experiences and insights of frontline clinicians been sought.

We greatly value your input, and we hope you will be in a position to complete and return the enclosed survey. The survey has been piloted to ensure that it is clear, focussed and relevant. It may take 5-10minutes of your time and your response will be helpful and greatly appreciated in this project. The survey seeks to describe the experiences of clinicians only, and no identifiable patient data is sought. You have been included in this survey, as your name was identified as part of a random sample generated from the national Cervical Check listing.
In order to obtain a good response rate, further mailings will be sent, however, if you respond and or, would prefer not to receive any further mailings, simply use your practice stamp on the back of the stamped addressed envelope.

If you have any questions regarding this research please contact me by telephone or by email.

Many thanks for your time,
Sincerely yours,

Ms Hazel Ní Chonchubhair	Dr Brendan O Shea	Professor Kevin Conlon
RGN, PhD Candidate	Lecturer Public Health & Primary Care	Professor of Surgery

nichonh@tcd.ie
01-8964173 / 085-7088120

Appendix D. General Practitioner survey

DEMOGRAPHICS / PRACTICE CHARACTERISTICS

1. Please identify the number of GPs in your main centre of practice (including full time and part time)

   _____

2. Does your practice include a GP register?
- Yes
- No

3. Does your practice take undergraduate medical students?
- Yes
- No

4. Which term best describes your location?
- Rural
- Mixed
- Urban

5. Which best describes your practice demographics?
- Affluent
- Middle Income
- Deprived

   AND
- Young
- Middle Aged
- Older

6. Please state your gender:
- Male
- Female

7. Please state your age group:
- <25
- 26-33
- 34-42
- 43-51
- >52

8. How many years have you worked in general practice since completing your training?
- 0-3 years
- 4-8 years
- >8 years

CHRONIC PANCREATITIS IN YOUR PRACTICE

1. Please estimate the total number of patients attending your practice with Chronic Pancreatitis
- 0
- 1-3

- 4-5
- 5-10
- >10

2. Are you happy to consider providing ongoing care to patients with Chronic Pancreatitis?

   Very Unhappy 1 2 3 4 5 6 7 8 9 10 Very Happy

3. Do you code your patients with chronic pancreatitis in your electronic medical record?

- Yes
- Sometimes
- Never

4. How would you rate am online CME module on the primary care management of pancreatitis ancreatitis

Limited Use 1 2 3 4 5 6 7 8 9 10 Very Useful

MANAGEMENT OF CHRONIC PANCREATITIS

1. Do you patients have easy access to a specially-dedicated multi-disciplinary team for the management of their Chronic Pancreatitis?

- Yes
- No
- Unsure

2. If your patients do have access to a dedicated team, is this team led by a:

- Surgeon
- Intensivist
- Other (Please Specify)
- Unsure

3. Are you aware of any national or international consensus guidelines for the management of chronic pancreatitis?

- Yes
- No

4. If yes – please specify any chronic pancreatitis guidelines of which you are aware

   _____
   _____
   _____

5. Is there any particular area of chronic pancreatitis management that you think could be improved on in the Primary Care setting?

   _____
   _____
   _____

6. Can you list any barriers to good care which patients with Chronic Pancreatitis encounter in the Primary Care setting?

7. Would a **disease registry** be useful to estimate chronic pancreatitis prevalence in Ireland?

- Yes
- No
- Unsure

8. Do you think a national chronic pancreatitis **disease registry** would be utilised by health professionals?
- Yes
- No
- Unsure

9. What would be the benefits of such a **disease registry**?
   Please comment
   _____
   __

10. Please specify any **barriers** that you perceive might affect utilisation of such a registry
    _____
    _____
    _____
    _____

MANAGEMENT OF ACUTE PANCREATITIS

1. Do you see patients with **acute pancreatitis**?
- Yes
- No

2. Are there follow-up procedures in place for **acute pancreatitis** patients in your practice?
- Yes
- No
- Unsure

SURVEY COMPLETE

Thank you for taking the time to complete this survey.

Kind regards,
Hazel Ní Chonchubhair & Dr Brendan O'Shea
The University of Dublin, Trinity College
Departments of Surgery & Public Health and Primary Care
Room 1.29, Trinity Centre for Health Sciences
Adelaide & Meath Hospitals incorporating the National Children's Hospital
Tallaght
Dublin 24

Tell: +353 1 8961000,

Appendix E. Sample letter for participation in the SIBO study

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

PRIVATE & CONFIDENTIAL

DATE:

Dear,

I am writing to you because you had a previous admission to Tallaght Hospital with a diagnosis of Chronic Pancreatitis and I wish to invite you to participate in a study on bowel health.

From previous research, we know that chronic pancreatitis is a growing problem in Ireland. We also know that some symptoms may be caused by different bacteria in patient's small bowel. To better understand this, we are recruiting patients for a study to see if you have surplus bacteria in your small bowel, which may be linked to difficulties with digestion, absorption and overall disease

This will involve the following:

- **A breath test (which requires you to fast and then drink a sugary drink for testing)**
- **Some questionnaires (about your demographics, symptoms, quality of life, smoking/alcohol)**

This would all take place during one appointment. We would ask you to attend Tallaght Hospital and we would explain the project to you in details.

This study is being carried out as part of my research towards my PhD and by doing this we hope to improve the knowledge of chronic pancreatitis and ultimately improve the service to patients in Ireland and Internationally.

All tests will be done free of charge.
If you are interested in participation, or if you have any further questions, please call 01-8964173, 01-8963179 or email nichonh@tcd.ie.

Appointments are held on weekday mornings and at a time convenient to you.

Kind Regards,

Hazel Ní Chonchubhair
PhD Candidate
Trinity Centre for Health Sciences,
Tallaght Hospital
01-8964173

Marie Egan
Clinical Nurse Specialist
Pancreas & Bilary Diseases
Tallaght Hospital
01-4143361

Prof Kevin Conlon
Professor of Surgery
Consultant Surgeon
Tallaght Hospital
01-8963719

Appendix F. Patient information leaflet SIBO study

Small Intestinal Bacterial Overgrowth in Chronic Pancreatitis
Patient Information leaflet

1. **Title of study:**
   Small intestinal bacterial overgrowth in chronic pancreatitis

2. **Introduction:**

   We know from previous studies that chronic pancreatitis is a growing problem in Ireland. We want to conduct a study to see if you have surplus bacteria in your small bowel, which may be linked to difficulties with digestion, absorption and overall disease.

3. **Procedures:**

   If you wish to be included in the study, you will be asked to participate by phone / postal contact or by attending one of our clinics.
   (1) For the small intestine bacterial overgrowth study, you will have to take a drink containing a sugary substance of about 250mls and then provide a breath test over a number of hours.

In addition to the study, you will be asked questions about;

- Quality of life
- Employment - days lost from work / study
- Smoking / alcohol status / history
- Pancreatic Enzyme Replacement Therapy (PERT)
- Access to specialist services (pancreas specialists / nutrition / dietetics services / smoking cessation / alcohol avoidance / social work)
- Clinical data
- Demographics (age / gender / ethnicity / geographical location)

4. **Benefits:**

   You may or may not benefit from your participation in the study, but the information we ascertain may help create a profile of patients with chronic pancreatitis that may be used to help improve services. The identification of any potential problems will allow clinicians to commence appropriate and effective therapies, potentially halting further problems through early diagnosis and identifying if their symptoms are made worse by differences in bacterial overgrowth. The information you provide is valuable to our work.

5. **Risks:**

   There are no risks in this study as we are assessing only

6. **Exclusion from participation:**

   You will not be able to partake in this study if you've a known malabsorbtive condition such as coeliac disease or irritable bowel disease, or if you have had previous major abdominal surgery. You must be an adult strictly >18 years of age and you must be able to give informed consent.

7. **Alternative treatment:**

   If you are not part of this study, you will be assessed as normal, and as deemed appropriate by the medical team

8. **Confidentiality:**

   Your identity will remain confidential. Your name will not be published and will not be disclosed to anyone outside the hospital. The exception of this will be bloods or stool samples sent to accredited laboratories outside Tallaght hospital, which have an identifier.

9. **Compensation:**

   Your doctors are covered by standard malpractice insurance. Nothing in this document restricts or curtails your rights

10. **Voluntary participation:**

    You have volunteered to participate in this study. You may quit at any time. If you decide not to participate, or if you quit, you will not be penalised and will not give up any benefits which you had before entering the study

11. **Stopping the study:**

    You understand that your doctor / nurse or sponsoring company may stop your participation in the study at any time without your consent

12. **Permission:**

    This study has been approved by the chairman of the Joint Research Ethics Committee of Tallaght Hospital and St James' Hospital (AMNCH/SJH JREC)

13. **Further information:**

    You can get further information or answers to your questions about the study, your participation in the study, and your rights, from Ms Hazel Ní Chonchubhair who can be telephoned at 01-8964173, or emailed at nichonh@tcd.ie. If members of your team learn of important new information that might affect your desire to remain in the study, he or she will tell you

Appendix G. User agreement for HIPE access

Health Intelligence Ireland
Information Governance – User Agreement

Purpose

Health Intelligence Ireland supports the quest for better health for patients, their families and the population. It provides controlled web access to health related data, analyses and maps to inform the planning, safe delivery and quality assurance of services, and to enable epidemiology and research.

Terms of agreement

1. Data is exclusively used for the above purpose.
2. The confidentiality and privacy of data are respected in accordance with the provisions of data protection and other relevant legislation.
3. Usernames and passwords are not shared with others.
4. The user is fully responsible for the analysis and interpretation of results – with special care being taken in light of the quality of the data (such as its completeness, accuracy or timeliness).
5. External reports, presentations or publications do not contain data that could directly or indirectly identify individual patients (e.g. cells with 4 or fewer cases where such data alone or combined with other data could compromise individual confidentiality) are not shown.
6. Data is not used for record linkage purposes, or to identify/contact patients, or shared with third parties unless appropriate information governance/data protection/ethical processes have been followed.
7. In any output: the source(s) of the data source/s are appropriately acknowledged together with the wording "Accessed using Health Intelligence Ireland"; map/report Z/R and licence number(s) and the Health Intelligence Ireland logo and any system accreditations remain on any outputs. Following publication, a copy/reference is forwarded to Health Intelligence Ireland and the relevant data source/s as a matter of courtesy.
8. Health Intelligence Ireland is informed should data quality or analysis issues be identified.
9. The user informs the Group Controller (see below) when their details or role requires updating or inactivation.
10. The Group Controller is responsible for enabling and maintaining appropriate role-based user access.

Health Intelligence Ireland creates the Agency folder (e.g. national body) giving access to the Agency Controller/s. The Agency Controller creates a Section Folder/s (e.g. department/programme) giving access to the Section Controller/s. The Section controller creates a Group folder/s (e.g. team/laboratory) giving access to the Group folder Controller/s. The Group Controller provides user access to the analytical and display tools.

I understand and agree to abide by the above conditions

USER

Role/s ☐ Viewer ☐ •**Analyst** ☐ Export ☐ See identifiers ☐ Controller

First name (print) HAZEL Surname (print) NÍ CHONCHUBHAIR

Job title PHD STUDENT (FULL TIME) Email NICHONH@TCD.IE

IP address (Internet) IPv4: 134.226.180.22

Work address THE UNIVERSITY OF DUBLIN, TRINITY COLLEGE, DEPARTMENT OF SURGERY, ROOM 1.29, TRINITY CENTRE FOR HEALTH SCIENCES, ADELAIDE AND MEATH HOSPITAL INCORPORATING THE NATIONAL CHILDREN'S HOSPITAL, TALLAGHT, DUBLIN 24.

Office phone no/s. 01-8961000 Mobile no. 085-7088120

Signed HAZEL NÍ CHONCHUBHAIR *Date* 20/08/2014

HEAD OF DEPARTMENT / SECTION / UNIT

First name (print) KEVIN CHRISTOPHER Surname (print) CONLON

Job title PROFESSOR OF SURGERY Email CONLONK@TCD.IE

Work address THE UNIVERSITY OF DUBLIN, TRINITY COLLEGE, DEPARTMENT OF SURGERY, ROOM 1.36, TRINITY CENTRE FOR HEALTH SCIRNCES, ADELAIDE AND MEATH HOSPITAL INCORPORATING THE NATIONAL CHILDRENS HOSPITAL, TALLAGHT, DUBLIN 24.

Office phone no/s.01-8963719 Mobile no. 087-2157207

Signed KEVIN CONLON *Date 20/08/2014*

CONTROLLER

First name (print) Surname (print)

Job title Email

Work address

User Agreement - HII 281111-7

Appendix H. Patient consent form SIBO study

SJH / AMNCH RESEARCH ETHICS COMMITTEE.
CONSENT FORM

Title of research study:

An investigation of small intestine bacterial overgrowth in patients with chronic pancreatitis

This study and this consent form have been explained to me. My doctor has answered all my questions to my satisfaction. I believe I understand what will happen if I agree to be part of this study.
I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights. I have received a copy of this agreement and I understand that, if there is a sponsoring company, a signed copy will be sent to that sponsor.
Name of sponsor:

PARTICIPANT'S NAME:

PARTICIPANT'S SIGNATURE:

Date:
Date on which the participant was first furnished with this form:

Where the participant is incapable of comprehending the nature, significance and scope of the consent required, the form must be signed by a person competent to give consent to his or her participation in the research study (other than a person who applied to undertake or conduct the study). If the subject is a minor (under 18 years old) the signature of parent or guardian must be obtained:-

NAME OF CONSENTOR, PARENT or GUARDIAN:
SIGNATURE:
RELATION TO PARTICIPANT:

Where the participant is capable of comprehending the nature, significance and scope of the consent required, but is physically unable to sign written consent, signatures of two witnesses present when consent was given by the participant to a registered medical practitioner treating him or her for the illness.

NAME OF FIRST WITNESS: SIGNATURE:

NAME OF SECOND WITNESS: SIGNATURE:

Statement of investigator's responsibility: I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Physician's signature:
Date:
(Keep the original of this form in the participant's medical record, give one copy to the participant, keep one copy in the investigator's records, and send one copy to the sponsor (if there is a sponsor).

3

Appendix I. Sample letter for participation genetic study

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

PRIVATE AND CONFIDENTIAL

Chronic pancreatitis genetic study

DATE:

Dear,

I am writing to you because you had a previous admission to Tallaght Hospital and I wish to invite you to participate in a study.

From previous research, we know that patients with chronic pancreatitis may have different genetic mutations compared to people without the disease. To better understand this, we are recruiting patients for study.

This will involve the following:

- A blood test to assess for specific pancreatic genetic mutations

This would all take place during one quick appointment (approximately 15 minutes). We would ask you to attend Tallaght Hospital and we would explain the project to you in details.

This study is being carried out as part of my research towards my PhD and by doing this we hope to improve the knowledge of chronic pancreatitis and ultimately improve the service to patients in Ireland and Internationally.

All tests will be done free of charge.

If you are interested in attending the appointment, or if you have any further questions, please call 01-8964173, or email nichonh@tcd.ie.

Kind Regards,

Hazel Ní Chonchubhair	Marie Egan	Prof Kevin Conlon
PhD Candidate	Clinical Nurse Specialist	Professor of Surgery
Trinity Centre for Health Sciences,	Pancreas & Bilary Diseases	Consultant Surgeon
Tallaght Hospital	Tallaght Hospital	Tallaght Hospital
01-8964173	01-4143361	01-8963719

Appendix J. Patient information leaflet genetic study

An investigation of genetic mutations in an Irish cohort of chronic pancreatitis patients

Patient Information leaflet

1. **Title of the study:** An investigation of genetic mutations in an Irish cohort of chronic pancreatitis patients

2. **Introduction:**
   Patients that have been diagnosed with chronic pancreatitis and have volunteered to be included in the study will be further assessed by genetic testing. By doing this, we will see if specific genes variants common to Ireland (such as the cystic fibrosis gene variants) are partly responsible for the incidence of chronic pancreatitis in Ireland. Cystic fibrosis (CF) gene mutation testing is performed for the purpose of a diagnosis of cystic fibrosis or to determine if you are a carrier.

3. **Procedures:**
   You will be asked to give a **blood sample** and some of the bloods will be sent to accredited laboratories outside of Tallaght Hospital and St Vincent's University Hospital for testing (where tests are not done here onsite)
   - You will be asked to complete some **questions about lifestyle, quality of life, smoking, alcohol use** and a **cystic fibrosis specific questionnaire**
   - The lead investigator (Hazel Ní Chonchubhair) would like permission to look at your **medical notes, healthcare records and scans** to get as much relevant information as we can for the study
   - Following genetic testing, you will be offered a referral for **genetic counselling** if diagnosed with cystic fibrosis or as a cystic fibrosis carrier. This will take place in the National Centre for Medical Genetics at Our Lady's Children's Hospital Crumlin, or at the National Adult Cystic Fibrosis Unit at St. Vincent's University Hospital under the supervision of Professor Andrew Green and Professor Charles Gallagher. Genetic counsellors can explain how cystic fibrosis or cystic fibrosis gene mutations are inherited and offer further advice or assistance. If you are planning on having a child you should discuss this test and the test result with a genetic counsellor
   - We will also recruit controls which are people that do not have chronic pancreatitis for the purpose of comparison.
   - If you decide to be included in the study, you will be required to attend one appointment for assessment (usually Monday mornings). The appointment should take maximum of 1 hour where you will provide a blood sample and answer some questions about demographics, lifestyle and a quality of life questionnaire. The clinics are held in Tallaght Hospital and St Vincent's University hospital

4. **Benefits:**
   The main benefit to you is to find out whether you have cystic fibrosis or if you might be a carrier of a cystic fibrosis gene variant mutation. Although these findings are not reversible, this information is very valuable. You will get a report of your results, which will be copied to your consultant and / or GP if you agree

5. **Risks:**
   There are no risks in this study as we are assessing only. However, receiving a diagnosis that you are a cystic fibrosis gene mutation carrier or that you in fact have cystic fibrosis, can be a traumatic experience, one filled with uncertainty, fear and denial. The incidence of cystic fibrosis is approximately 1 in 1461 in Ireland, and approximately 1 in 19 Irish people carry a cystic fibrosis mutation. If partners each carry a cystic fibrosis mutation they have a 1 in 4 chance for each pregnancy of having a child with cystic fibrosis. If you have a relative who has cystic fibrosis or is known to carry a mutation of the gene your chances of carrying a mutation are greater because of your family's history.

   We will refer patients with positive genetic mutations for assessment in either the National Centre for Medical Genetics at Our Lady's Children's Hospital Crumlin, or at the National Adult Cystic Fibrosis Unit at St. Vincent's University Hospital. You will be referred for specialised care by well-trained cystic fibrosis professionals. If after receiving your test results, you feel that you would benefit from further genetic counselling this can be arranged by us. Genetic counsellors can explain how cystic fibrosis or cystic fibrosis gene mutations are inherited and offer further advice on and assistance. If you are planning to have a child you should discuss this test and the results with a genetic counsellor.

6. **Exclusion from participation:**
   You may not participate in this study if you have a known diagnosis of cystic fibrosis or pancreatic cancer or if you are currently pregnant. You must be an adult strictly >18 years of age and you must be able to give informed consent.

7. **Alternative treatment:**
   If you are not part of this study, you will be assessed as normal by your doctor as deemed appropriate by the medical team

8. **Confidentiality:**
   Your identity will remain confidential. Your name will not be published and will not be disclosed to anyone outside the hospital. The exception to this will be that blood samples sent to accredited laboratories outside of Tallaght Hospital and St. Vincent's University Hospital will have an identifier. Any information received will be used purely in the interests of drug safety

9. **Compensation:**
   Your doctors / nurses / dieticians are covered by standard malpractice insurance. Nothing in this document restricts or curtails your rights

10. Voluntary Participation:

You have volunteered to participate in this study. You may quit at any time. If you decide not to participate, or if you quit, you will not be penalised and will not give up any benefits which you had before entering the study

11. Stopping the study:

You understand that your doctor/nurse/dietician may stop your participation in the study at any time without your consent

12. Permission:

This study has been approved by the chairman of the Joint Research Ethics Committee of Tallaght Hospital and St. James Hospital (JREC AMNCH/SJH)

Further information: You can get more information or answers to your questions about the study, your participation in the study, and your rights, from Ms. Hazel Ní Chonchubhair who can be telephoned at 01-8964173, or emailed at nichonh@tcd.ie. If members of your team learn of important new information that might affect your desire to remain in the study, he or she will tell you.

Appendix K. Consent form genetic study

SJH / AMNCH RESEARCH ETHICS COMMITTEE.
CONSENT FORM

Title of research study:
An investigation of genetic mutations in an Irish cohort of chronic pancreatitis patients

This study and this consent form have been explained to me. My doctor has answered all my questions to my satisfaction. I believe I understand what will happen if I agree to be part of this study.
I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights. I have received a copy of this agreement and I understand that, if there is a sponsoring company, a signed copy will be sent to that sponsor.
Name of sponsor:

PARTICIPANT'S NAME:

PARTICIPANT'S SIGNATURE:

Date:
Date on which the participant was first furnished with this form:

Where the participant is incapable of comprehending the nature, significance and scope of the consent required, the form must be signed by a person competent to give consent to his or her participation in the research study (other than a person who applied to undertake or conduct the study). If the subject is a minor (under 18 years old) the signature of parent or guardian must be obtained:-

NAME OF CONSENTOR, PARENT or GUARDIAN:
SIGNATURE:
RELATION TO PARTICIPANT:

Where the participant is capable of comprehending the nature, significance and scope of the consent required, but is physically unable to sign written consent, signatures of two witnesses present when consent was given by the participant to a registered medical practitioner treating him or her for the illness.

NAME OF FIRST WITNESS: SIGNATURE:
NAME OF SECOND WITNESS: SIGNATURE:

Statement of investigator's responsibility: I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Physician's signature:
Date:
(Keep the original of this form in the participant's medical record, give one copy to the participant, keep one copy in the investigator's records, and send one copy to the sponsor (if there is a sponsor).

Appendix L. SVUH patient information leaflet / consent form genetic study

St. Vincent's Healthcare GROUP LIMITED

ELM PARK, DUBLIN 4

PLEASE INSERT NAME & ADDRESS OF DEPARTMENT

PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE:

An investigation of genetic mutations in an Irish cohort of chronic pancreatitis patients

(*a genetic mutation occurs when a DNA gene is damaged or changed in such a way as to alter the genetic message carried by that gene)

NAME OF PRINCIPAL INVESTIGATOR: Professor Kevin Conlon

You are being invited to participate in a research study. Thank you for taking time to read this.

WHAT IS THE PURPOSE OF THIS STUDY?

We want to examine patients with chronic pancreatitis to see if they have genetic mutations that might make them more susceptible to developing chronic pancreatitis. By doing this, we will see if specific genes common to Ireland (such as the cystic fibrosis gene) are partly responsible for the incidence of chronic pancreatitis in Ireland. Cystic fibrosis (CF) gene mutation testing is performed for the purpose of a diagnosis of CF or to determine if you are a carrier.

WHY HAVE I BEEN CHOSEN

You have been chosen because you have been diagnosed with chronic pancreatitis and you wish to be included in this study to be assessed by having genetic testing.

WHAT WILL HAPPEN IF I VOLUNTEER?

Your participation is entirely voluntary. If you initially decide to take part you can subsequently change your mind without difficulty. This will not affect your future treatment in any way. Furthermore your doctor may decide to withdraw you from this study if, he/she feels it is in your best interest.
If you agree to participate, you will be requested to
Procedures:

- You will be asked to give a **blood sample** and some of the bloods will be sent to laboratories outside of Tallaght Hospital and St Vincent's University Hospital for testing (as the genetic testing takes place in laboratories in St James's Hospital and in The National Centre for Medical Genetics, Our Lady's Children's Hospital Crumlin)
- You will be asked to complete some **questions about lifestyle, quality of life, smoking, alcohol use** and a **cystic fibrosis specific**

questionnaire. You will also be asked some questions about your demographics, your age, sex, ethnicity, your address, your level of education and marital status. This is to help us profile patients so we can better describe potential findings and compare and contrast the findings with other countries.

- The lead investigator (Hazel Ní Chonchubhair) would like permission to look at your **medical notes, healthcare records and scans** to get as much relevant information as we can for the study
- Following genetic testing, you will be offered a referral for **genetic counselling** if diagnosed with cystic fibrosis or as a cystic fibrosis carrier. This will take place in the National Centre for Medical Genetics at Our Lady's Children's Hospital Crumlin, or at the National Adult Cystic Fibrosis Unit at St Vincent's University Hospital under the supervision of Professor Andrew Greene and Professor Charles Gallagher. Genetic counsellors can explain how cystic fibrosis or cystic fibrosis gene mutations are inherited and offer further advice and assistance. If you are planning on having a child you should discuss this test and the test results with a genetic counsellor
- We will also recruit controls which are people that do not have chronic pancreatitis, for the purpose of comparison

If you decide to be included in the study, you will be required to attend one appointment for assessment (usually Monday or Friday mornings). The appointment should take maximum of 1 hour where you will provide a blood sample and answer some questions about demographics, lifestyle and a quality of life questionnaire. The clinics are held in Tallaght Hospital and St Vincent's University hospital.

ARE THERE ANY BENEFITS FROM MY PARTICIPATION?

There may be benefits for all chronic pancreatitis patients present and future in Ireland. We will ascertain information and a profile of patients which can be used to improve services.

ARE THERE ANY RISKS INVOLVED IN PARTICIPATING?

There are no risks in this study as we are assessing only. You might experience slight discomfort when obtaining a blood sample. However, receiving a diagnosis that you are a cystic fibrosis gene mutation carrier or that you in fact have cystic fibrosis, can be a traumatic experience, one filled with uncertainty, fear and denial. The incidence of cystic fibrosis is approximately 1 in 1461 in Ireland, and approximately 1 in 19 Irish people carry a cystic fibrosis mutation. If partners each carry a cystic fibrosis mutation they have a 1 in 4 chance for each pregnancy of having a child with cystic fibrosis. If you have a relative who has cystic fibrosis or is known to carry a mutation of the gene your chances of carrying a mutation are greater because of your family's history.

We will refer patients with positive genetic mutations for assessment in either the National Centre for Medical Genetics at Our Lady's Children's Hospital Crumlin, or at the National Adult Cystic Fibrosis Unit at St. Vincent's University Hospital. You will be referred for specialised care by well-trained cystic fibrosis professionals. If after receiving your test results, you feel that you would benefit from further **genetic counselling** this can be arranged by us. Genetic counsellors can explain how cystic fibrosis or cystic fibrosis gene mutations are inherited and offer further advice and assistance. If you are planning to have a child you should discuss this test and the test results with a genetic counsellor.

WHAT HAPPENS IF I DO NOT AGREE TO PARTICIPATE?

If you decide not to participate in this study your treatment will not be affected in any way.

CONFIDENTIALITY

Your identity will remain confidential. A study number will identify you. Your name will not be published or disclosed to anyone.

COMPENSATION

Your doctors / nurses / dieticians are adequately insured by virtue of their participation in the clinical indemnity scheme. Nothing in this document restricts or curtails your rights

WHO IS ORGANISING AND FUNDING THIS RESEARCH?

This study is organised and funded by

Mylan Pharmaceuticals

Will I be paid for taking part in this study?

Participation is voluntary and no payment (monetary or otherwise) will be provided for participation and no expenses will be reimbursed. All costs including assessments, investigations and procedures relevant to the study will be met by the Department of Surgery / Industry funding .

Will my expenses be covered for taking part in this study?

No, as above.

HAS THIS STUDY BEEN REVIEWED BY AN ETHICS COMMITTEE?

The St. Vincent's Healthcare Group, Ethics and Medical Research Committee have reviewed and approved this study.

CONTACT DETAILS

If you have any questions about the study please contact lead investigator Hazel Ní Chonchubhair on:

Phone – 01-8964173 (research office)
Email – nichonh@tcd.ie

PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

- I have read and understood the Participant Information YES ☐ NO ☐
- I have had the opportunity to ask questions and discuss the study YES ☐ NO ☐
- I have received satisfactory answers to all my questions YES ☐ NO ☐
- I have received enough information about this study YES ☐ NO ☐
- I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care YES ☐ NO ☐
- I agree to take part in the study YES ☐ NO ☐

Participant's Signature: _____ Date: _____

Participant's Name in print: _____

Investigator's Signature: _____ Date: _____

Investigator's Name in print: _____

Appendix M. Subject suitability screening document – SIBO and genetic studies

Subject suitability screening form

Chronic Pancreatitis Microbiome, SIBO and genetic study

Recruited as patient ☐ **control** ☐

Confirm patient is adult >18years of age ☐

For patients

Does the patient have a diagnosis of idiopathic or alcohol-induced chronic pancreatitis ☐

How was this diagnosis made?

_____

Referring consultant

_____

Checklist*

Was this subject included in other CP studies?	☐
Has this subject had a major gastrointestinal resection?	☐
Does this subject have a malabsorptive condition (IBD/Coeliac disease)?	☐
Does the subject have cystic fibrosis?	☐
Does the subject have pancreatic cancer?	☐
Is subject pregnant?	☐
Does subject have prognosis of <6months?	☐

**Not eligible if yes to any of these questions*

Eligible for study: Yes ☐ **No** ☐

Appendix N. Patient assessment form – SIBO and genetic studies

FRONT SHEET

Assessment form

Chronic Pancreatitis SIBO / Genetic study

Complete this standard assessment for all subjects

Date _/_ /20___ Completed by _____

Recruited as patient ☐ control ☐

Affix addressograph or print name, MRN, DOB, Address

Patient to be included in:

1. SIBO study ☐

2. Genetics study ☐

Tick as appropriate ☐

Informed consent obtained ☐ *File in patient folder*

Inclusion/exclusion criteria	☐	Included in the study	☐
Consented for study	☐	Excluded from the study	☐
>18 years	☐		
No prognosis of <6 months	☐		
Subject not pregnant	☐		

Assessment form
CP recruitment studies
Hazel Ní Chonchubhair

Addressograph

Page 2

Best contact number

_____

GP name _____

GP address

_____

_____

Agrees to copy of letter to GP? Y / N

Gender Male / female

Age _____

Ethnicity _____

Date of 1st presentation with chronic pancreatitis / date of diagnosis with chronic pancreatitis

Hospital stay in the last 12 months? **YES** ☐ **NO** ☐ **Days** ☐

Aetiology of chronic pancreatitis

Alcohol ☐

Idiopathic ☐

Other ☐ **Specify** _____

Diagnosis of chronic pancreatitis *(see appendix X for diagnostic details)*

ERCP ☐

MRCP ☐

CT ☐

MRI ☐

Other ☐ **Specify** _____

Severity (e.g. Cambridge) _____

Assessment form
CP recruitment studies
Hazel Ní Chonchubhair

Addressograph

Page 3

Employment status

- Working full-time ☐
- Working part-time ☐
- Retirement due to age ☐
- Retirement due to illness ☐
- Prolonged unemployment ☐

Co-morbid disease

- Diabetes ☐
- Cardiovascular ☐
- PUD / GORD ☐
- Pulmonary ☐
- Hepatic ☐
- Renal ☐
- Other ☐

Pain Score *see 10 point visual analogue scale*

☐

Marital status

- Single ☐
- Married / living with partner ☐
- Divorced / separated / widowed ☐

Education level *(highest level completed)*

- Primary ☐
- Secondary ☐
- University ☐

Assessment form
CP recruitment studies
Hazel Ní Chonchubhair

Addressograph

Weight
Kg to the nearest 0.1, light clothes, no shoes

Height
M to the nearest 0.1, no shoes

Body mass index (BMI)
Weight (Kg) / Height (m^2)

Alcohol

Current drinker
Ex-drinker
Never drinker

How many drinks per week? Types? Frequency?

_____

Grams alcohol per week

_____

Smoking

Current smoker
Ex-smoker
Never smoker

How many per day or per week? For how many years?

_____

Pack – year history *(*1 pack year - 20 cigarettes per day for 1 year)*

_____

Assessment form
CP recruitment studies
Hazel Ní Chonchubhair

Addressograph

Supplementation		Details
Supplement use (Y / N)	☐	
Sip feed	☐	
Fat soluble vitamin	☐	
Iron	☐	
Calcium	☐	
Calcium/Vitamin D	☐	
Zinc	☐	

Pancreatic enzyme replacement therapy (PERT)

Yes ☐ **No** ☐

Amount and frequency per day *(e.g. 40,000 with bfast, 25,000 with lunch, 60,000 with dinner)*

Medications / Antibiotics / Prokinetics / Probiotics / Laxitives

Access to specialist services

Have you seen a specialist pancreatic team (before this appointment)

_____

_____

Have you seen a specialist pancreatic dietitian? _____

Any other notes or comments

_____

_____

_____

_____

_____

Appendix O. Poster advertising for controls SIBO study

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

SMALL INTESTINAL BACTERIAL OVERGROWTH STUDY

VOLUNTEERS NEEDED

We are looking for male smokers to take part in a research study as controls

- **Study involves a fasting hydrogen breath test to detect bacterial overgrowth and some quality of life questions**
- **You will need to come in to Tallaght Hospital for an appointment one morning**
- **All tests are free of charge (voucher for lunch in the canteen provided for the study day)**

Profile required (approximate age)

Age 45 Male – Smoker (x 3 volunteers needed)
Age 43 Male – Smoker
Age 47 Male – Smoker
Age 27 Male – Smoker
Age 58 Male – Smoker
Age 69-79 years Male – Smoker

To volunteer or for more information please contact:

Hazel Ní Chonchubhair: 01-8964173 or nichonh@tcd.ie

Study approved by the Joint Tallaght Hospital / St James Hospital Ethics Committee, and supervised by Professor Kevin Conlon

Appendix P. Breath testing assessment form SIBO study

Bacterial Overgrowth

NAME _____ DOB _____

ADDRESS _____ MALE /FEMALE _____

_____

_____

DATES _____ MRN _____

WEIGHT _____ HEIGHT _____

SYMPTOMS:

Excess wind / flatulence ☐

Abdominal bloating / distention ☐

Diarrhea ☐

Constipation ☐

Abdominal Pain ☐

Weight loss ☐

Body aches ☐

Fatigue ☐

BREATH 1(BASELINE) TIME 0:

DRINK SUBSTRATE (250ml Glucose):

BREATH 2 TIME 20 :

BREATH 3 TIME 40 :

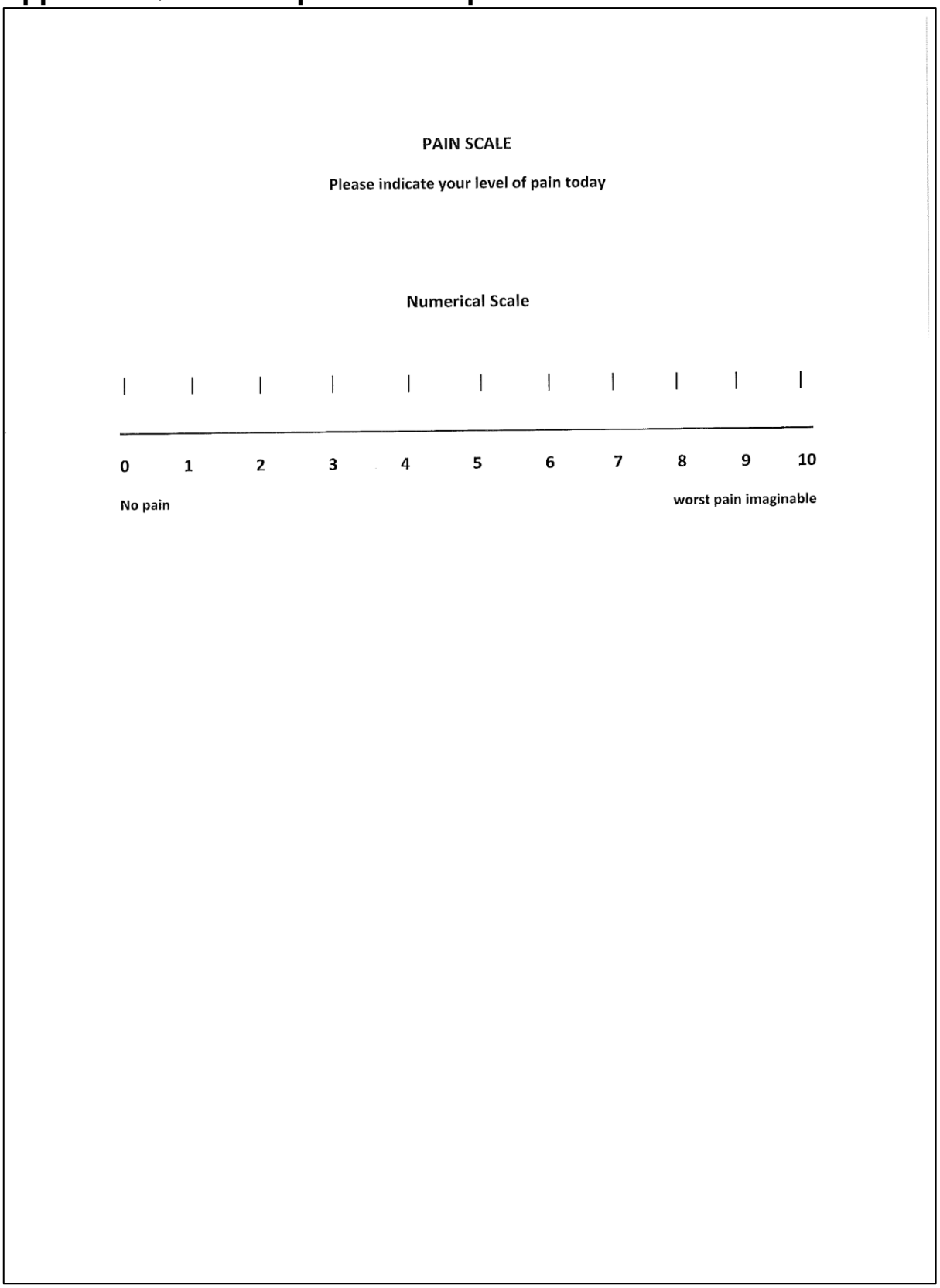
BREATH 4 TIME 60 :

BREATH 5 TIME 80 :

BREATH 6 TIME 100:

BREATH 7 TIME 120 :

Appendix Q. Chronic pancreatitis pain scale



Appendix R – DNA extraction protocol

Manual Extraction of DNA from 1-5ml Blood Sample

1. Approximately 2-3mls of 1X RBC Lysis solution to the tube to remove the entire contents of the tube, using a pastette
2. Invert the rack/tubes 30 times.
3. Allow to incubate at room temperature for 10 minutes.
4. Spin the samples at 3000g for 10 minutes.
5. Pour off the supernatant
6. Add 5mls to Cell Lysis Solution
7. Vortex the tubes and allow to sit at room temperature
   24 hours, vortex the tubes again
8. Add 1.66mls of Protein Precipitation solution to the tubes
9. Shake vigorously for 3 minutes.
10. Add 5mls of 100% Isopropanol to the Qubes.
11. Add 67µls of glycogen (20mg/ml) to the qube
12. Shake for 3minutes, spin at 3000g for 5 minutes.
13. Pour the supernatant from the sample tube into the qube
14. Invert 30 times
15. Spin the qubes at 3000g for 5 minutes.
16. Pour off the supernantant,
17. Add 5mls of 70% Ethanol to the qubes.
18. Spin the qubes at 3000g for 5 minutes.
19. Pour off the supernantant
20. Invert the qubes for 2-3 minutes and then allow the sample to air dry for 2-3 minutes.
21. Add the chosen volume of 1X TE buffer
22. Incubate at 65°C for 1 hour.
23. Allow to cool.
24. Spin at 3000g for 1 minute. Leave overnight.
25. Transfer DNA to labelled 2ml tube. Allow to incubate at room temperature at least overnight on the platform rocker.
26. Read DNA concentration on the Nanodrop.