Clinical and Pathological aspects of Pancreatitis

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Clinical and Pathological aspects of Pancreatitis

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"Am Anfang schaute ich mich um, konnte aber den Wagen, von dem ich träumte nicht finden. Also beschloss ich, ihn mir selbst zu bauen."

Prof.Dr.Ing. h.c. Ferry Porsche (1948)

CONTENTS

INTRODUCTION

INTRODUCTION

History of the Pancreas and Pancreatitis

The pancreas was apparently first described by Herophilus, a Greek anatomist and surgeon, who was born in 336 BC. Four hundred years later, Ruphos, in the 1st or 2nd Century AD, an anatomist – surgeon of Ephesus, proposed the name "pancreas". In Greek, the word means "all flesh". Scientific study of the pancreas began in 1642, when Johann Georg Wirsüng, discovered the pancreatic duct in the San Francisco Monastery in Padua, Italy (Figure 1.). Wirsüng was murdered by a student the year after the discovery[1].

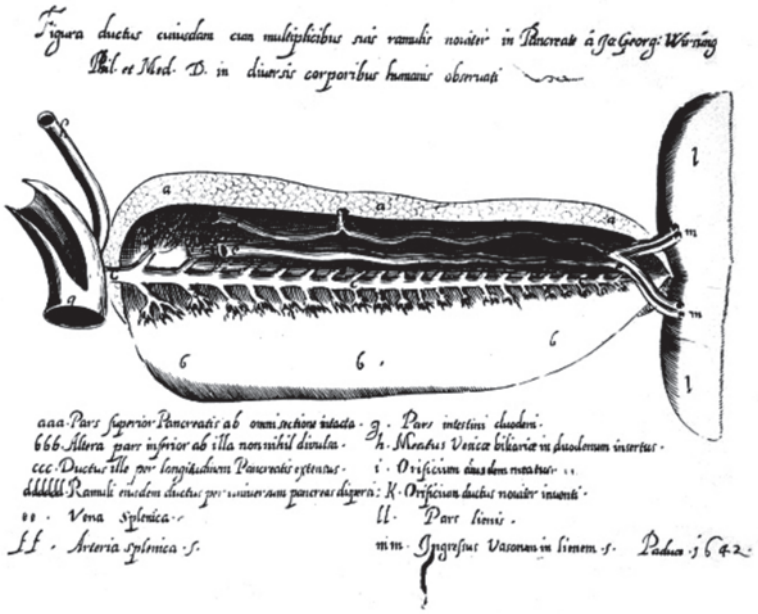

Figure 1 Imprint by Wirsung from a copper plate (1642)

The history of "acute pancreatitis" probably starts with the fatal illness of Alexander the Great (323 BC)[2]. The first systematic analysis of acute pancreatitis was performed by Reginald Huber Fitz (1843-1913), a pathologistat the Massachusetts General Hospital. He published a landmark paper on acute pancreatitis in the Boston Medical and Surgical Journal in 1889[3]. This study described the clinical characteristics of 53 patients, distinguishing between the haemorrhagic, suppurative and gangrenous forms of the disease. He believed that acute pancreatitis was a complication of

gastroduodenitis and 'originates by the extension of a gastroduodenal inflammation along the pancreative duct'. It was Chiari who, in 1896, postulated that the underlying pathophysiological mechanism of the disease was pancreatic autodigestion-i.e. that the pancreas 'succumbs to its own digestive properties'[4].

Definition and cause of pancreatitis

In this thesis, acute pancreatitis is defined as proposed in the 1992 Atlanta classification: "An acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems, associated with raised pancreatic enzyme levels in blood and/or urine"[5]. Chronic pancreatitis is defined as a continuing inflammatory disease of the pancreas characterized by irreversible morphologic changes that typically cause pain and/or permanent loss of endo/exocrine function[28].

Epidemiology and etiology of acute pancreatitis

Worldwide the annual incidence rate of acute pancreatitis ranges from 5 to 80 per 100.000 and tends to increase over time, with a reported case-fatality rate ranging from 3% to 10.7%[6]. In the Netherlands, the annual incidence is 19.2 per 100000[7].
Sex is strongly associated with the risk of acute pancreatitis: the incidence of alcoholic pancreatitis is higher in men and the incidence of gallstone pancreatitis is higher in women[6]. The two major etiological factors responsible for acute pancreatitis are alcohol and cholelithiasis (gallstones) accounting for 70-80% of all cases[6]. Other etiologies are: abdominal injury, ischemia, surgery, ERCP +/- endoscopical sphincterotomy (ES), exacerbation of chronic pancreatitis, pancreatic cancer, anatomical variants of the pancreas/biliary system, autoimmune diseases, hyperlipidemia, hypocalcaemia, drugs, toxins, infections, genetic and idiopathic[6].

New insights regarding acute pancreatitis

Recent papers report a higher incidence of non-biliary acute pancreatitis and an increased transition from acute pancreatitis to chronic pancreatitis in cigarette smokers[8-16]. More and more evidence is accumulating, regarding the influence of obesity on the incidence and course of the disease[17-22]. Therefore, smoking and obesity are important in patient's management and pancreatitis research.

OUTLINE OF THE THESIS

This thesis deals with two focus areas in pancreatology.

1. Clinical studies on acute biliary- and drug induced pancreatitis.
2. Clinico-morfological studies on pancreatic steatosis and pancreatic inflammation/fibrosis.

Part 1: Clinical studies: acute biliary pancreatitis and drug induced pancreatitis

A biliary origin is prevalent in the majority of cases presenting with acute pancreatitis. Unlike alcohol induced acute pancreatitis (the second most common cause of pancreatitis), biliary or gallstone pancreatitis can possible be treated by means of an endoscopical intervention: Endoscopic Retrograde Cholangiography- (ERC). The merits of this treatment are still debated in several studies, symposia and guidelines. In the first part, a review of the etiology, diagnosis, treatment and recurrence of ABP is presented (**Chapter 1, 2 and 4**). The opinion of Dutch gastro-enterologists regarding the role of an early ERC and Endoscopic Sphincterotomy (ES) in acute biliary pancreatitis was studied by means of a national survey (**Chapter 3**). These studies combined with a prospective trial from the Dutch Acute Pancreatitis Group[23] form the basis of the APEC-trial, a large nationwide prospective randomized trial comparing an emergency ERCP versus conservative treatment in ABP starting in 2013. This study will hopefully provide a definite answer regarding the role of early ERC in biliary pancreatitis.

Reports of drug-induced acute pancreatitis (AP) have been published since the 1950s, and each year the list of drugs associated with AP expands. The etiology of drug-induced acute pancreatitis remains unclear. Even when a definite association has been demonstrated it is often impossible to determine whether only drug exposure or interaction with the underlying condition is the cause of pancreatitis (e.g. azathioprine and Crohns disease or pentamidine and HIV). Results from several reports point to a higher incidence of thiopurine induced acute pancreatitis in Crohn's disease compared to ulcerative colitis or other disease[24,25]. The overall incidence probably ranges from between 1.2% and 1.4% of pancreatitis cases[6,26]. The drugs reported to be associated with the highest incidence of acute pancreatitis are: mesalazine (HR 3.5) azathioprine (HR 2.5), simvastatine (HR 1.8) and didanosine[6].

In a gastroenterology-liver patient population, thiopurines are used in various disease including Crohn's disease, ulcerative colitis, undifferentiated colitis, micro-scopical colitis, refractory celiac disease, auto-immune hepatitis and pancreatitis. In **chapter 5** we investigate the association proclaimed "disease associated sensitivity" to develop thiopurine induced acute pancreatitis in patients with Crohn's disease compared to ulcerative colitis and vasculitis.

The interval between drug administration and the onset of acute pancreatitis differs depending on the drug, and therefore may be helpful in establishing a causal relation between drug and onset of pancreatitis. Certain drugs, such as paracetamol (acetaminophen), can cause pancreatitis after a single dose. Others, such as azathioprine, 6-mercaptopurine, metronidazole, aminosalicylates, and sulfonamides,

characteristically can cause acute pancreatitis within a month after exposure, while still others, such as pentamidine, valproic acid, and didanosine, appear to cause injury weeks or months after exposure, possibly through the accumulation of a toxic metabolite[27]. The interval time between starting thiopurines and the development of acute pancreatitis (latency-time) is studied in **chapter 5.**

Part 2: Clinicomorfological studies on pancreatic steatosis and inflammation/fibrosis

Pancreatic steatosis

Pancreatic steatosis was first described by Ogilvie in 1933[29]. He observed an association between fatty infiltration of the pancreas and obesity: obese cadavers had 17% pancreatic fat, while lean cadavers had only 9% fat[29]. Other associations with pancreatic steatosis include: age, impaired glucose in tolerance / type 2 diabetes mellitus, hepatic steatosis and alcohol use[30-32]. In **chapter 7** a review of the clinical associations/ impact and nomenclature of pancreatic fatty infiltration is given.

Pitt postulated that central obesity leads to organ steatosis[33]. Like pancreatic steatosis, hepatic steatosis is related to obesity[34]. A more severe form of fatty infiltration of the liver is nonalcoholic steatohepatitis (NASH) which leads to cirrhosis in 20% of the patients[34]. In analogy of NASH, the identity "non-alcoholic steatopancreatitis (NASP)" could excist[33]. In **chapter 6** the relation between NAFLD/ NASH and obesity versus the development of pancreatic steatosis (or NASP) is studied in a post-mortum histological study of both organs.

Obesity is associated with an increased risk of acute pancreatitis and an aggravated course of pancreatitis[17-22]. The mechanisms by which obesity increases the severity of acute pancreatitis are unclear. Several hypotheses have been suggested:
(1) central obesity leads to organ steatosis and altered serum adipokines including reduced adiponectin and markedly elevated leptin. This abnormal adipokine milieu results in increased tissue infiltration of monocytes and macrophages which produce proinflammatory cytokines that alter organ function[33]; (2) Pancreatic injury leads to a massive release of pancreatic lipase that causes digestion of (peri)pancreatic adipose tissue, which becomes infiltrated by significant quantities of monocytes (inflamed and necrotic adipose tissue). Because adipocytes synthesize and secrete adipose-specific proteins (adipocytokines), such as adiponectin, leptin, and resistin, have potent immunomodulatory and metabolic activities, the metabolic and pro-inflammatory changes seen in acute pancreatitis might be – at least in part – caused by these proteins[35]; (3) obese patients have an increased accumulation of fat within and around the pancreas where necrosis is often located[36].

It must be kept in mind that the incidence of (predicted severe) acute pancreatitis is increased in obese patients[17-22]. The observational studies and meta-analyses did not stratify for the predicted severity, which leads to an overrepresentation of obese patients with a predicted severe disease. This will eventually lead to a more severe course of acute pancreatitis in obese patients. In **Chapter 8** we study the unselected true effect of obesity and several anthropometric parameters on the morbidity of acute pancreatitis in patients with a predicted severe acute pancreatitis.

Pancreatic inflammation/ fibrosis

There is strong epidemiological evidence for cigarette smoking as a risk factor for pancreatic cancer. Smokers have a two- to three-fold risk compared to nonsmokers and the risk remains elevated up to two decades after cessation of smoking and lower the age of pancreatic cancer presentation[37-40]. Cigarette smoking is also an independent risk factor in the development of acute and chronic pancreatitis[41,42]. Furthermore, smoking accelerates the progression of chronic pancreatitis[43,44]. Malfertheiner contrived a theory that the risk of smoking for pancreatic cancer and chronic pancreatitis development can be reconciled by the fact that chronic pancreatitis independent of its etiology represents a pre-cancerous condition[45]. Hence, it is assumable that tobacco smoke induces chronic inflammation as a trigger for cancer development. His theory is confirmed by two observations on rat pancreata exposed to cigarette smoke. Both studies revealed clear signs of inflammation after cigarette smoke exposition[46,47]. Malfertheiner's theory is tested in **chapter 9**, a post-mortum study, in which the extent of fibrosis was scored on the pancreata of smokers and non-smokers.

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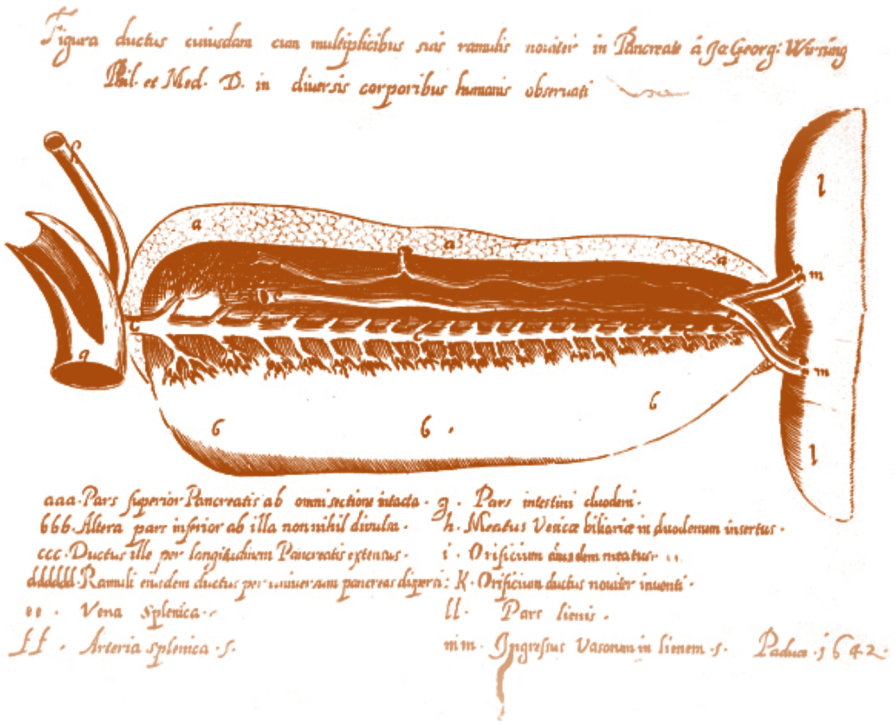
PART 1

CLINICAL STUDIES ON ACUTE BILIARY AND DRUG INDUCED PANCREATITIS



CHAPTER 1

ETIOLOGY AND DIAGNOSIS OF ACUTE BILIARY PANCREATITIS

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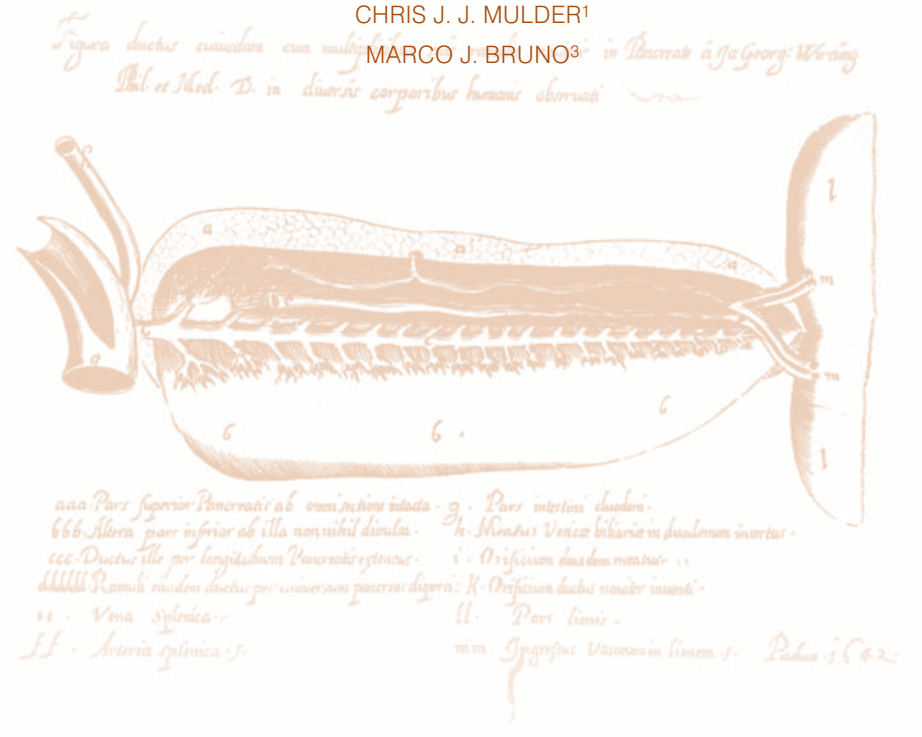

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ABSTRACT

Establishing a biliary etiology in acute pancreatitis is clinically important because of the potential need for invasive treatment, such as endoscopic retrograde cholangiopancreatography.

The etiology of acute biliary pancreatitis (ABP) is multifactorial and complex. Passage of small gallbladder stones or biliary sludge through the ampulla of Vater seems to be important in the pathogenesis of ABP. Other factors, such as anatomical variations associated with an increased biliopancreatic reflux, bile and pancreatic juice exclusion from the duodenum, and genetic factors might contribute to the development of ABP.

A diagnosis of a biliary etiology in acute pancreatitis is supported by both laboratory and imaging investigations. An increased serum level of alanine aminotransferase (>1.0 μkat/l) is associated with a high probability of gallstone pancreatitis (positive predictive value 80–90%). Confirmation of choledocholithiasis is most accurately obtained using endoscopic ultrasonography (EUS) or magnetic resonance cholangiopancreatography (MRCP).

This Review discusses the pathogenesis of ABP and the clinical techniques used to predict and establish a biliary origin in patients with suspected ABP.

INTRODUCTION

Gallstones are present in 35–60% of patients with acute pancreatitis in the USA and Western Europe (1-3). Most cases of acute pancreatitis are mild and self-limiting; however, approximately 25% of patients with acute pancreatitis develop multiple organ failure and severe biliary pancreatitis, such as necrotizing pancreatitis (1-4). The overall worldwide mortality rate for acute pancreatitis ranges between 2% and 10% and has decreased since the 1970s and 1980s, presumably because of advances in intensive care support, the use of broad-spectrum antibiotics, percutaneous drainage of infected peri-pancreatic collections and a decrease in the indiscriminate use of surgical procedures during the acute phase of the disease (1,5).

The yearly incidence of acute biliary pancreatitis (ABP) is estimated to be 4.9–80.0 cases per 100,000 people with distinct variation in people from different ethnic backgrounds—predominantly affecting white individuals and individuals with a Hispanic back- ground (5). Over the past decade, the incidence of ABP has increased by 35% in countries such as the Netherlands and the USA (5). The incidence of ABP is higher in women than in men (69% versus 31%), and increases with age (a greater than threefold increase in the incidence of ABP is observed at 75 years of age compared with 20 years of age (5).

Biliary pancreatitis is the first manifestation of gallstone disease in up to 40% of patients who do not have a preceding 'warning' episode of biliary colic (5). Between 4% and 8% of patients with gallstones eventually develop biliary pancreatitis secondary to migratory gallstones (6). ABP potentially requires invasive treatment (that is, endoscopic retrograde cholangiopancreato- graphy [ERCP]), demonstrating the clinical importance of establishing a biliary origin of acute pancreatitis. The controversial role of an emergency ERCP in ABP means that clear etiopathological insight and diagnosis of ABP are crucial for future intervention studies on this disease.

This review discusses the pathogenesis of ABP, including the role of genetics, ductal anatomy and ampullary obstruction in development of the disease. In addition, methods that predict and establish a biliary etiology in patients with suspected ABP (such as evaluations of serum biochemistry and imaging) will also be discussed.

REVIEW CRITERIA

This Review is based on the personal experience of the authors and literature accumulated over their years working on acute biliary pancreatitis. The authors compiled their literature lists independently, and searched the PubMed database for articles published between 1970 and 2009 using the terms "(gallstone OR

biliary) AND pancreatitis AND (prediction OR origin OR algorithm) NOT (chronic OR carcinoma OR autoimmune OR case report)", which resulted in 407 hits, and "(gallstone OR biliary) AND pancreatitis AND (etiology OR etiology OR pathogenesis) NOT (carcinoma OR autoimmune OR case report)", which resulted in 196 hits. The PubMed title and abstract results were scanned manually resulting in a possible 120 articles of potential interest. Only full text papers in English, German and Dutch were reviewed. The reference lists of selected papers were examined for leads to relevant older literature.

PATHOGENESIS

Investigations over the past 100 years have shown that the pathogenesis of ABP is multifaceted (Figure 1). The first association between gallstones and acute pancreatitis, was proposed by Bernard in 1856 (7). This hypothesis was supported by observations published in 1901 by Opie; he observed an impacted gallstone at the papilla of Vater (also known as the major duodenal papilla) in two patients with severe pancreatitis (8). In the same year, Halstead suggested that reflux of bile into the pancreatic duct caused pancreatitis in patients with cholelithiasis (9).

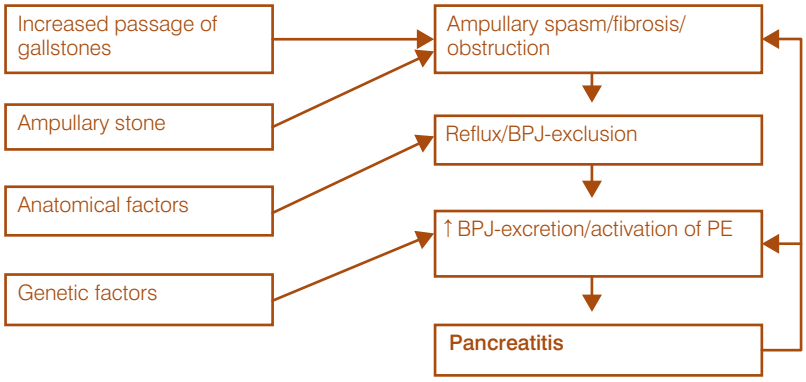

Figure 1 Pathogenesis of acute biliary pancreatitis

The pathogenesis of acute biliary pancreatitis is multifaceted. Anatomical, genetic and stone-related factors are all involved in the development of the disease. Passage of gallstones through the ampulla of Vater and the presence of mainly small gallstones can lead to ampullary spasm, fibrosis and obstruction of the hepatopancreatic ampulla. This obstruction can lead to biliopancreatic reflux and the exclusion of bile and pancreatic juices (which is further exacerbated by abnormal anatomy). Ultimately, elevated levels of bile and pancreatic juices and activation of pancreatic enzymes lead to pancreatitis. Abbreviation: BPJ, bile–pancreatic juice.

Subsequently, in 1980, Acosta and colleagues proposed that pancreatic inflammation is aggravated by persistent ampullary obstruction by gallstones (10). Additionally, a 'multihit model' was proposed by Neoptolemos, who postulated that repeated episodes of ampullary obstruction by gallstones contribute to initiation of ABP (11).

Pancreatic duct obstruction

Gallstone impaction usually causes a transient obstruction; most of the offending stones migrate rapidly and can be found in the stool of patients with ABP (12,13). Studies in opossums have indicated that multiple changes to the pancreas, biliary tract and small intestine occur after biliary obstruction, including: acinar cell necrosis and pancreatic edema, increased pancreatic secretion (from the exocrine glands), increased levels of bile acid in the pancreatic juice, reduced myoelectric activity of the sphincter of Oddi and the duodenum, increased levels of bacterial trans location from the gut to the intestinal lymph nodes, endotoxemia, and blockade of the reticuloendothelial system (14–20). Interestingly, in animal models of pancreatitis, the above mentioned factors, did not cause severe necrotizing pancreatitis when experimentally combined with pancreatic duct obstruction. Experimental (15,21) and clinical (10,22–24) evidence demonstrates that ampullary obstruction by gallstones not only initiates, but also sustains and aggravates biliary pancreatitis. Gallstones in the common bile duct have been found in many patients who died from biliary necrotizing pancreatitis (25,26). The exact mechanisms by which gallstones passage through the ampulla of Vater and then initiate pancreatic inflammation remains elusive. Biliary sludge containing minute calculi seem to cause no clinical harm as they pass the ampulla of vater, but both biliary sludge and microscopic granules have been shown to initiate acute idiopathic pancreatitis (27,28). However, only 2% of patients who have undergone extracorporeal lithotripsy of gallstones develop mild pancreatitis, irrespective of the initial size of the gallstone before therapy despite the fact that countless parts of fragmented gallstones pass the ampulla of Vater (29). even if the hepato-pancreatic ampulla is not obstructed by a sizable stone, the passage of sludge or small stones may induce local edema or a transient spasm of the ampulla of Vater that leads to temporary obstruction of the pancreatic duct. the causative role of transient obstruction by gallstones or biliary sludge in pancreatitis is supported by the observation that attacks of recurrent biliary pancreatitis are prevented or largely reduced by endoscopic sphincterotomy (29,30). These studies also demonstrate that endoscopic sphincterotomy can be used as an alternative to cholecystectomy in patients with biliary pancreatitis (30,31).

Duodenal exclusion of bile and pancreatic juice

In 1991, murayama *et al (*32). first reported a relationship between duodenal bile exclusion and exacerbation of acute pancreatitis as a result of their experiments in rats that had temporary obstruction of both the main pancreatic duct and the common bile duct (32). The researchers observed increased serum levels of circulating cholecystokinin in rats with obstructions in both the main pancreatic duct and common bile duct compared to rats with an obstruction in the common bile duct alone. Only a combination of main pancreatic duct and common bile duct obstruction induced acute pancreatitis (33). In rats, cholecystokinin-releasing peptide is secreted into the duodenum and degraded by trypsin (34). A lack of trypsin (induced by ligation or obstruction of the main pancreatic duct) will cause an increased amount of cholecystokinin-releasing peptide and subsequent increased cholecystokinin production (34). Cholecystokinin acts on the CCK_A-receptors and induces exocrine pancreatic juice production (35). Previously, discussions about the translation of the above mentioned physiological pathways to humans were questioned by the lack of evidence of direct cholecystokinin-induced stimulation of human pancreatic acinar cells (36). However, in 2008, murphy *et al.*37 discovered that cholecystokinin has a direct effect on human pancreatic acinar cells and activates calcium signaling and stimulates enzyme secretion in these cells (37). Additionally, in experimental studies in rats, duodenal bile and pancreatic juice depletion combined with ampulla of vater obstruction causes stress on the acinar cell and results in an increased production of activated stress kinases (such as p38 mitogen- activate protein kinases and extracellular signal-regulated kinases), which aggravates ABP (35,38–40).

Gallstone-related factors

Stone-related features have been identified as potential risk factors for the development of ABP, including small size (<2–5 mm), multiplicity, mulberry shape and irregular surface (41–48). Observations in humans indicate that small gallstones, excess cholesterol crystals in the gallbladder and good emptying of the gallbladder are particularly associated with an increased risk of pancreatitis (5,49). In a multivariate analysis of 143 patients with gallstones (43 patients with ABP; 100 control patients without ABP), small gallstone diameter (that is, a diameter of ≤5 mm), cystic duct width (that is, a diameter of >5 mm) and gallstone number (that is, ≥20 gallstones) were shown to be substantial risk factors for ABP (50). All these factors relate to the ease by which gallstones are able to migrate from the gallbladder to the common bile duct and the number of stones that pass through the ampulla.

Biliopancreatic reflux

In addition to obstruction causing an increase in intra-pancreatic pressure, reflux of infected bile (infected with bacteria such as *Escherichia coli*) into the pancreatic duct has been proposed to be a plausible mechanism through which pancreatitis is initiated (51). Under physiological circumstances, the pressure in the pancreatic duct is threefold higher than in the common bile duct (52), thereby preventing reflux of bile into the pancreatic duct. During times of ampullary obstruction the pressure gradient between the biliary tree and the pancreatic duct may reverse (as demonstrated in rabbits) (53). The causative role of the composition of the refluxate has been investigated in animal studies (54,55) and in patients with pancreatic disorders (56,57). Sterile refluxate caused an increase in the permeability of the pancreatic ductal system via activation of pancreatic enzymes (54–56), whereas only infected bile (infected with *Escherichia coli*) or a mixture of pancreatic juice and bile caused pancreatitis (52).

Ductal anatomy

The relationship between ductal anatomy, biliary origin, and severity of pancreatitis has not been studied extensively. Several anatomical factors have been linked to an increased incidence of ABP, including an enlarged common bile duct (>1.3 mm) and a wide angle between the bile duct and the pancreatic duct (37° versus 24° in patients with non-ABP choledocystolithiasis)(41). Jones and colleagues found that 67% of patients with aBP had a common pancreaticobiliary channel as opposed to 32% of patients with cholelithiasis or choledocholithiasis without biliary pancreatitis (57). This finding was confirmed by Kamisawa *et al.*(58). in a prospective study of 354 patients who underwent ERCP a common pancreaticobiliary channel was observed in 11.5% of patients with ABP, which was significantly more frequent than n patients without pancreatitis (4.9%, P <0.05)(58). Even in patients with totally separate orifices of the common bile duct and pancreatic duct, gallstone pancreatitis can occur (57). Obviously, in this case, reflux of bile into the pancreatic duct is excluded as a contributing factor. In such cases, in our experience, obstruction of the pancreatic duct might occur if a stone is wedged at the level of the ampulla of vater, in much the same way as a cystic duct stone can cause obstruction of the common bile duct in Mirrizzi syndrome. One may question whether drainage of pancreatic juice via the minor pancreatic (or santorini) duct serves as a pivotal escape route and overflow protection mechanism in case of obstruction of the major pancreatic (or Wirsung) duct at the level of the major duodenal papilla. Uomo and co-workers studied the morphology of the pancreatico–choledochal junction and the pancreatic ductal system by comparing the findings from ERCP in 62 patients with ABP and 62 patients as controls (59). Of note, more abnormalities of the ampulla of Vater were observed in the ABP group (that is, edema, hemorrhagic

lesions, lacerations, and impacted stones) than in the controls (66% versus 33.5%, $P = 0.001$). Papillary diverticula were found in 19% of patients with ABP and in 6.4% of the control group (59). In this series, no substantial differences were observed between the length of the common pancreaticobiliary channel, the angle between the common bile duct and the main pancreatic duct and the patency of the Santorini duct. Furthermore, noappreciable difference in Santorini duct patency was found between edematous and necrotizing cases of ABP. Contradictory results were, however, reported by Nowak and colleagues (60) and Kamisawa *et al.*(61) these investigators observed a markedly lower frequency of Santorini duct patency in patients with ABP (17% and 8%) than in the control group (69% and 43%, $P < 0.001$ and $P < 0.01$, respectively); patients with other causes of acute pancreatitis also had low frequency of Santorini duct patency. The control group in both studies was comprised of patients with suspected biliary disease in whom a pancreaticogram was obtained during ERCP. Based on a study in rabbits, Arendt postulated that a patent Santorini duct might protect the pancreas from the harmful consequences (increased intraductal and, hence, increased parenchymal pressure) of obstruction of the main pancreatic duct, but it might also promote biliary pancreatic reflux during obstruction of the common channel and lead to subsequent development of pancreatitis caused by infected choledochal secretions(62).

Genetics

Over the past 10 years variations or mutations in the genes that encode pancreatic enzymes have been suggested as potential risk factors for the development of acute pancreatitis (including ABP). The common pathological event in acute pancreatitis is the early activation of zymogens within the pancreatic parenchyma. In this regard, the activation of trypsinogen by enteric peptidases to trypsin is important, as trypsin is capable of converting all proteolytic precursor enzymes (phospholipase, chymotrypsin and elastase) to their active form and activates other cascades (including complement, kinin–kallikrein, coagulation and fibrinolysis signaling cascades)(63). Several trypsinogen mutations have been identified in patients with chronic, hereditary pancreatitis (64). A number of mechanisms exist to protect the pancreas from autodigestion. One of these mechanisms is the synthesis of pancreatic secretory trypsin inhibitor (also known as serine protease inhibitor Kazal-type 1), which is a potent inhibitor of the trypsin activity within the pancreas and is encoded by *SPINK1*. research into the genetics of ABP is limited. one study reported a higher incidence of *SPINK1* mutations (101a>G, which results in a Asn34Ser variant in the protein) in patients with acute pancreatitis (all causes) compared with a healthy control group (24 out of 936 versus 18 out of 2234, odds ratio 3.240, $P < 0.001$) (65). A second study reported a case of recurrent ABP associated with a mutation in *ABCB4* (the genetic defect was a heterozygous

3,683–3,688 del within exon 28 of *ABCB4*) (66). *ABCB4* encodes multidrug resistance protein 3, a protein involved in the transport of phosphatidylcholine across the canalicular membrane of the hepatocyte. Gene defects in *ABCB4* have been associated with progressive familial intrahepatic cholestasis type 3, intra- hepatic cholestasis of pregnancy, adult biliary cirrhosis and the newly described low phospholipid-associated cholelithiasis syndrome (66). Mutations in the cystic fibrosis transmembrane regulator (*CFTR*) gene have been extensively described in patients with chronic pancreatitis (mainly alcoholic origin) and in recurrent idiopathic acute pancreatitis (64,67–69. CFTR is located in the proximal ductal system of the pancreas and regulates bicarbonate secretion (64) Disturbances in the secretion of bicarbonates can theoretically lead to enhanced viscosity of pancreatic secretions, possibly resulting in protein plugs that might contribute to the progression of chronic pancreatitis (64). However, an increased prevalence of mutations in *CFTR* have not been reported in patients with ABP.

DIAGNOSIS

Acute pancreatitis is most reliably diagnosed using the classification proposed by the Atlanta Pancreatitis Classification working Group in 2008 (70). These criteria include: acute abdominal pain and rebound tenderness in the upper abdomen, increased pancreatic enzyme levels (amylase or lipase) in blood, urine or ascitic fluid (at least threefold greater than normal limits), and abnormalities characteristic of acute pancreatitis as determined by radiological findings. To establish a diagnosis of acute pancreatitis, two or more of the above criteria must be fulfilled while other causes of acute abdominal pain are excluded, such as: gastric perforation, acute cholecystitis, acute cholecystolithiasis and an acute myocardial infarction. Distinguishing biliary pancreatitis from other forms of acute pancreatitis can be difficult and requires biochemical and radiological evaluations (Figure 2). Additionally, the presence of gallstones alone might suggest a biliary origin, although this finding is not conclusive.

BIOCHEMISTRY

Diagnostic criteria

Determination of serum levels of amylase or lipase are used in the diagnosis of acute pancreatitis. serum lipase and amylase concentration rise within 4–8 h after the onset of an attack of acute pancreatitis, peak after 24 h and return to normal levels after 2–4 days (amylase) or 8–14 days (lipase) (71). in most studies, diagnosis of acute pancreatitis is based on high levels (threefold higher than the upper limit of

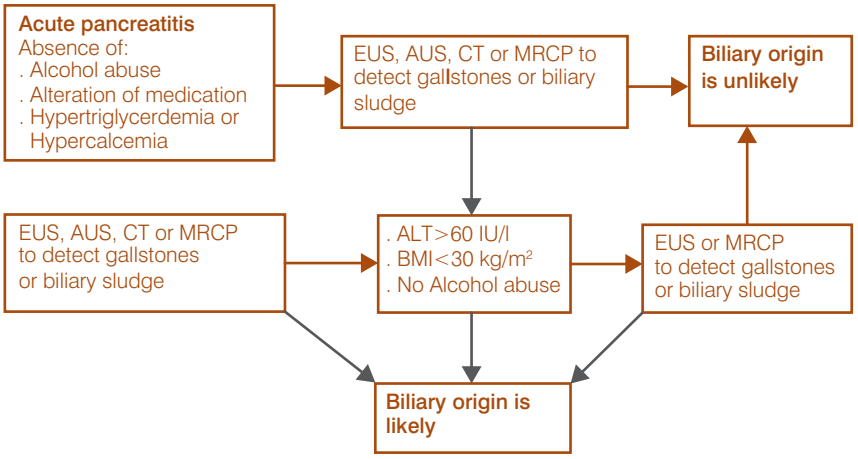

Figure 2 Predicting the biliary origin of acute pancreatitis

Biochemical and radiological evaluations can help to establish a biliary cause of acute pancreatitis. Confirmation of gallstones or biliary sludge using radiological imaging (including EUS, AUS, CT and MRCP), elevated serum levels of ALT (>60 IU/l) and a BMI <30 kg/m² indicates an episode of acute pancreatitis with a biliary origin. If these findings are negative another cause of acute pancreatitis should be considered.

Abbreviations: ALT, alanine aminotransferase; AUS, abdominal ultrasonagraphy; EUS, endoscopic ultrasonagraphy; MRCP, magnetic resonance cholangiopancreatography.

Gray arrow = yes, orange arrow = no

normal) of amylase (normal range 0.46–2.23 μkat/l) and lipase (0.5–3.2 μkat/l) (72). In fact, Lankisch and co-workers found that 21.9% of the patients who were eventually diagnosed with ABP had amylase levels less than three times the upper limit of normal at admission to the clinic (72). For lipase, 15.8% of patients who were later diagnosed with ABP had increased serum levels of the enzyme (72). For patients presenting with acute alcoholic pancreatitis, 41% and 15.7% had increased serum levels of amylase and lipase, respectively (lower than the recommended diagnostic criteria for the diagnosis of acute pancreatitis) (72). These findings indicate that tests for serum amylase and lipase must be repeated in cases where acute pancreatitis is suspected. Determination of the serum levels for lipase is preferred for the diagnosis of acute pancreatitis because of the high sensitivity and specificity, and long half-life of lipase in serum (7–13 h compared with the 2 h half-life of amylase), especially in patients with acute alcoholic pancreatitis (72). Serum amylase levels are generally higher in patients with ABP than in patients with other forms of acute pancreatitis(73). Serum pancreatic enzymes are often slightly increased during chronic kidney disease (74) and serum amylase is increased in patients with diseases of the liver, salivary gland, lung and genitalia (75).

Predicting a biliary etiology

Mc Mahon and Pickford were the first to suggest that a rise in plasma levels of hepatic transaminases on the day of admission for pancreatitis was associated with a biliary origin (76). However, 10–15% of patients with ABP present with normal serum liver enzymes (bilirubin and alkaline aminotransferase [ALT]) (77). Davidson and Neoptolemos developed a test that measured serum levels of three liver enzymes, diagnostic for ABP (alkalinephosphatase >3.76 μkat/l, alt >1.25 μkat/l and bilirubin >40 μmol/l) (78). This three-factor test had similar sensitivity and specificity in predicting the biliary origin of acute pancreatitis as a single-marker test that measured ALT alone (>1.0 μkat/l) (78). Furthermore, Stimac and co-workers retrospectively analyzed 145 patients with acute pancreatitis and developed a score to differentiate between alcoholic and biliary pancreatitis (79). The score was based on six serum markers (amylase, alt, alkaline phosphatase, aspartate transaminase, lipase:amylase ratio, and mean corpuscular volume) and one urine marker (amylase) with one point being scored per item over a specific threshold value. The Stimac score was reported to have a positive predictive value (PPV) of 98% and a negative predictive value (NPV) of 77% in correctly distinguishing biliary pancreatitis from alcoholic pancreatitis, when a patient has scored four or more points (79). This scoring system was easy to use and has promising predictive values, but has not been re-evaluated in other series. Tenner and colleagues performed a meta-analysis of studies that used liver enzymes (bilirubin, alkaline phosphatase, alt and aspartate transaminase) in the prediction of a biliary origin of an attack of acute pancreatitis (80). The researchers deduced that a threefold or greater elevation in ALT levels had a PPV of 95% in diagnosing ABP (80), which was confirmed in subsequent Studies (81,82). In a series by Ammori *et al.*(83), a single test for ALT (>1.34 μkat/l) had a high sensitivity (91%), specificity (100%), PPV (100%) and NPV (86%) for the identification of a biliary cause of an acute pancreatitis attack (83). Combining abdominal ultrasonography (AUS) with evaluations of alt level (>1.34 μkat/l) improved results, albeit not substantially (98% sensitivity, 100% specificity,100% PPV and 96% NPV) (83). Interestingly, one patient who presented with an elevated ALT level, but negative results from both AUS and endoscopic ultrasonography (EUS), was confirmed to have cholelithiasis at postmortem examination. In two subsequent studies that used EUS as a reference examination, the value of elevated alt levels in the diagnosis of ABP was once again confirmed (84,85). A French prospective study included 213 patients with a first episode of acute pancreatitis (62% of whom had confirmed pancreatitis with a biliary origin) to examine the effectiveness of bioclinical markers in predicting ABP(84). ALT levels more than twofold the upper normal limit were set as the diagnostic criteria for the prediction of ABP, resulting in a sensitivity, specificity, PPV and NPV of 74%, 84%, 88% and 66%, respectively (84). For ALT levels more than threefold higher than the

upper normal limit, the sensitivity, specificity, PPV and NPV were 61%, 91%, 92% and 59%, respectively (84). A study from Hong Kong showed that female sex, age >58 years and an ALT level >2.50 μkat/l had a high sensitivity (93%) and accuracy (85%) in predicting a biliary cause of pancreatitis (85). We must stress that an elevated alt level also has many alternative diagnoses (mainly alcoholism, nonalcoholic steatohepatitis and viral hepatitis). For instance, in western europe and the usa the prevalence of obesity and their related liver diseases (that is, nonalcoholic fatty liver disease and nonalcoholic steatohepatitis) are increasing (86). Thus, when ALT level is used as a diagnostic marker for ABP, BMI must be accounted for when predicting a biliary origin to rule out any alternative diagnoses (Figure 2).

IMAGING STUDIES

Diagnostic criteria

In our experience, a diagnosis of acute pancreatitis is supported by distinct radiological features found on AUS, CT or MRI. The use of AUS is often limited by the presence of air-filled and fluid-filled loops of bowel that overlie the pancreas. AUSis well-suited to show (and follow) peripancreatic fluid collections. the most widely used method to establish and confirm a diagnosis of acute pancreatitis is Ct. Findings from CT in acute pancreatitis can be classified into pancreatic and peripancreatic changes (87). Pancreatic changes include parenchymal enlargement (either diffuse or localized), parenchymal edema and necrosis. Peripancreatic changes consist of blurring of fat planes, thickening of the facial planes and the presence of fluid collections. Contrast-enhanced mri and contrast-enhanced CT are of comparable diagnostic and prognostic value in acute pancreatitis (88,89). MRI and magnetic resonance cholangiopancreatography (MRCP) are more accurate than CT in detecting bile duct lithiasis, pancreatic hemorrhage, pancreatic ductal anatomy, necrosis in peripancreatic fluid collections, duodenitis and duodenal narrowing (88–91). MRI is inferior to CT in the detection of small gas bubbles and calcifications (90). EUS is a very sensitive technique for the visualization of pancreatic lesions, pseudocysts, stones of the common bile duct and pancreatic duct anatomy (92). Furthermore, a radiological evaluation can be useful in the prediction of the severity of an attack of acute pancreatitis. For example, the Balthazar score on abdominal CT (93) and the extrapancreatic inflammation on CT score on abdominal MRI (94) can be used to estimate the severity of an acute pancreatitis.

Predicting biliary etiology

A biliary origin of an acute pancreatitis attack may be suspected in the case of cholecystolithiasis or dilation of the biliary tree with or without choledocholithiasis.

A summary of the performances of various diagnostic modalities in the detection of choledocolithiasis in ABP is listed in table 1. AUS has a high specificity and relatively high sensitivity for the evaluation of cholecystolithiasis in acute pancreatitis (93,95,96); however, this technique has a low sensitivity for the detection of gallstones in the common bile duct in patients with ABP(97–100) EUS is regarded as the most sensitive and specific procedure (with high PPV and NPV) for the detection of choledocholithiasis and cholecystolithiasis in patients with or without ABP (99,101–104) and, like AUS, is an operator-dependent procedure (101). Additionally, ERCP is highly sensitive for confirming the diagnosis of cholelithiasis in patients with ABP (98,99,102) while MRCP has been shown to be highly sensitive and specific for gallstone detection. Abdominal CtThas a low sensitivity (40%) in predicting common bile duct stones in patients with ABP, which makes it a less accurate tool in differentiating biliary pancreatitis from the other origins (99). More promising results for the use of CT in diagnosing ABP were reported by Tse *et al. (*105). The researchers analyzed six prospective trials in which common bile duct stones were detected with high- resolution helical scans (hCTCs) combined with intra venously administered contrast agents (105) with a sensitivity of 87% and specificity of 97% in detecting common bile duct stones, which results in an accuracy of 96%, hCTCs could have equivalent accuracy as MRCP in the detection of choledocholithiasis. However, the studies included in the meta-analysis by Tse *et al.*(105) were performed in patients with suspected common bile duct stones scheduled for a cholecystectomy. A head-to-head comparison of MRCP and hCTCs is, therefore, needed to draw a definitive conclusion as to whether mrCP is equivalent or superior to hCTCs in detecting choledocholithiasis. Only one

Table 1 Detection of gallstones in patients with acute biliary pancreatitis

Technique (location of gallstone)	sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	references
AUS (gallbladder)	67–87	93	100	75–80	83, 95, 96
AUS (CBD)	20–50	83	67	38.5	97–100
Abdominal CT (CBD)	40	92	89	48	99
MRCP (CBD)	80–100	83–98	89	71–100	99, 100
ERCP (CBD)	90–100	92	95	85	85, 97–99, 103, 111
EUS (CBD)	91–100	85–100	92–98	88–92	85, 97–99, 103, 111

Abbreviations: AUS, abdominalultrasonography; CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopicultrasonography; MRCP, magnetic resonance cholangio-pancreatography; NPV, negative predictive value; PPV, positive predictive value.

prospective head-to-head study has directly compared multiple imaging modalities and evaluated their sensitivity and specificity for detecting choledocholithiasis (99). Using endoscopic extraction of a biliary stone as the reference standard, the relative sensitivity of AUS, CT, MRCP, ERCP and intra ductal endosonography for detecting bile duct stones was 20%, 40%, 80%, 90% and 95%, respectively.99 mrCP in patients with ABP (with intraoperative cholangiogram or ERCP as the golden standard for common bile duct stone detection) was found to have high sensitivity (94–100%) and specificity (91–98%) for the detection of choledocolithiasis (100,106). The American Gastroenterological Association, Japanese and Dutch guidelines advise an initial AUS or EUS in every patient who presents with an attack of acute pancreatitis (107–109). If the initial ultrasound images are inadequate or if a suspicion of gallstone pancreatitis remains, repeat AUS after recovery should be performed (as per the American Gastroenterological Association guideline) (109). This guideline also states that endoscopic ultrasonography can be used as an accurate alternative approach to screen for cholecystolithiasis and choledocholithiasis, either at admission to the clinic or thereafter (109). The Dutch and UK guidelines recommend MRCP in cases of persistent suspicion of a biliary origin of acute pancreatitis (108,110).

CONCLUSIONS

The etiology of ABP is complex and involves multiple contributory factors. The passage of numerous small gallstones or biliary sludge (which contains microscopic particulates) through the ampulla of Vater seems to be a major factor in the pathogenesis of ABP. Anatomical variations, such as the presence of a common pancreatico-biliary channel and the absence of a patent Santorini duct, raise the risk of pancreatic duct obstruction and increased intrapancreatic pressure, and Santorini ducts are less prevalent in patients with ABP. Refluxate of pancreatic and bile juices increases the permeability of the pancreatic ducts and, if infected, adds to the risk of developing ABP. Additionally, exclusion of bile and pancreatic juices, and genetic mutations in genes that encode pancreatic enzymes result in elevated levels of activated pancreatic enzymes in the pancreas. Combinations of these features probably render an individual more prone to the development of ABP. A possible biliary origin in patients presenting with an acute pancreatitis should be investigated using laboratory tests and imaging techniques. an increased ALT level above normal (>1.0 μkat/l on admittance to the clinic is associated with a high probability (PPV 80–90%) of gallstone ABP. Additional confirmation of choledocholithiasis is most accurately obtained using EUS or MRCP.

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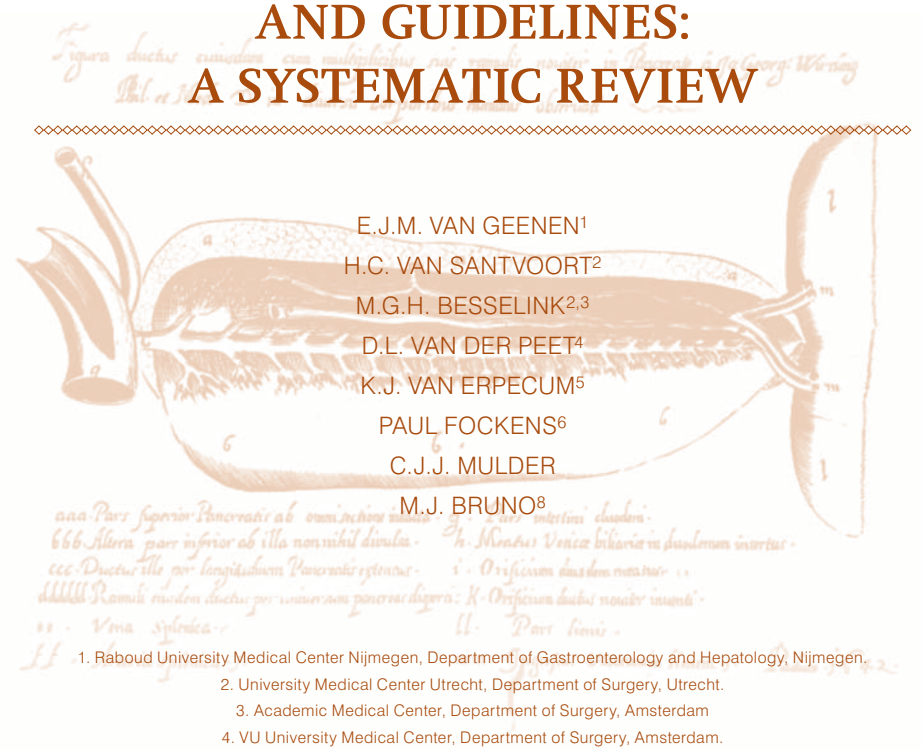
CHAPTER 2

LACK OF CONSENSUS ON THE ROLE OF ENDOSCOPIC RETROGRADE CHOLANGIOGRAPHY IN ACUTE BILIARY PANCREATITIS IN PUBLISHED META-ANALYSES AND GUIDELINES: A SYSTEMATIC REVIEW



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ABSTRACT

Objectives. Several randomized controlled trials studied the role of endoscopic retrograde cholangio pancreaticography (ERCP) and endoscopic sphincterotomy (ES) in acute biliary pancreatitis (ABP). No study assessed whether these trials resulted in international consensus in published meta-analyses and treatment guidelines.

Methods. A systematic review, according to the PRISMA-guidelines, of meta-analyses and guidelines on ERCP in ABP was performed in PubMed until August 2011.
The methodological quality of the meta-analysis and guidelines was assessed by a validated quality assessment tool.

Results. Eight meta-analyses and 12 guidelines fulfilled the inclusion criteria. There is consensus that ERCP is indicated in case of ABP with coexistent cholangitis and/or persistent cholestasis. By exception of the first meta-analysis, all included studies disapproved early ERCP in predicted mild ABP. Consensus is lacking regarding the role of early ERCP in predicted severe ABP, as 3 meta-analyses and 1 guidelines do not advice this strategy. Routine early ERCP in predicted severe ABP is recommend in 7 of the 11 guidelines.

Conclusions. There is consensus in guidelines and meta-analyses that ERCP/ES is indicated in patients with ABP and co-existing cholangitis and/or persistent cholestasis. Consensus is lacking on the role of routine early ERCP/ ES in patients with predicted severe ABP.

INTRODUCTION

Acute pancreatitis is a common disease with an estimated incidence of 30/100.000/year[1-3]. The leading etiology is gallstones/sludge, which accounts for 35-60% of acute pancreatitis cases in the United States and Western Europe[1-3]. Biliary pancreatitis is mostly mild and self- limited[1-3]. Some 15-20% of patients will develop severe acute biliary pancreatitis (ABP) including necrotizing pancreatitis and/or multiple organ failure[1-3].

In the Western world, the incidence of ABP has increased during the last decade by 35%[4-6]. Although mortality decreased by 35%, it still ranges from 2-14%, depending on patient age and decade of presentation[4,5,7,8]. Expedited triage of moderate to severe cases for more aggressive fluid resuscitation on admission and aggressive management in intensive care units (ICUs) are possible explanations for the declining mortality rates[6,9]. Keeping in mind that mortality does not differ between the various etiologies of acute pancreatitis [6,10-12], the outcome of treatment of ABP has probably truly improved over the last decades.

A treatment which might have contributed to better outcomes of ABP is emergency endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES), inspired by a landmark study of Neoptolemos et al in 1988[13]. The rationale for performing this study was based on several prevailing theories hypothesizing the merits of biliary decompression to ameliorate the severity of the pancreatitis, which include treatment and prevention of (ongoing) increased pressure in the pancreatic duct, (infected) bile reflux into the pancreatic duct, and stimulation of pancreatic enzyme production/activation by duodenal bile exclusion[14-19].

Based on the ampullary obstruction and reflux theory of Opie and Bernard, two surgical trials preceded the study of Neoptolomos[20,21]. In the years that followed, six randomized trials studied the effect of (early) biliary decompression versus conservative management on the course and outcome of patients with ABP[13,22-28]. These studies formed the basis for several meta-analyses and national guidelines. In the light of the somewhat confusing and partly conflicting outcomes of the various randomized trials we performed a systematic review to determine whether there is consensus in published meta-analyses and guidelines on the role of an (emergency) ERCP and ES in the early management of biliary pancreatitis.

METHODS

We conducted a systematic review of published English, German and French literature according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines[29,30]. The PRISMA Statement consists of a

27-item checklist and a four-phase flow diagram. The checklist includes items deemed essential for transparent reporting of a systematic review. The PRISMA flow diagram is shown in Figure1. Two PubMed searches were performed: 1. Meta-analysis; Emergency ERCP in ABP and 2. Guidelines: Emergency ERCP in ABP. One author (E.J.M.v.G.) performed the selection and reviewed all full text papers. The included and excluded studies were discussed with two other authors (H.C.v.S and M.J.B). Cross references were carefully reviewed.

Search for meta-analyses

For meta-analysis the subsequent search terms were used: "Pancreatitis AND (biliary OR gallstone OR gallstones OR cholelithiasis OR cholecystolithiasis)". The results were limited to articles published in the English language, and meta-analyses.

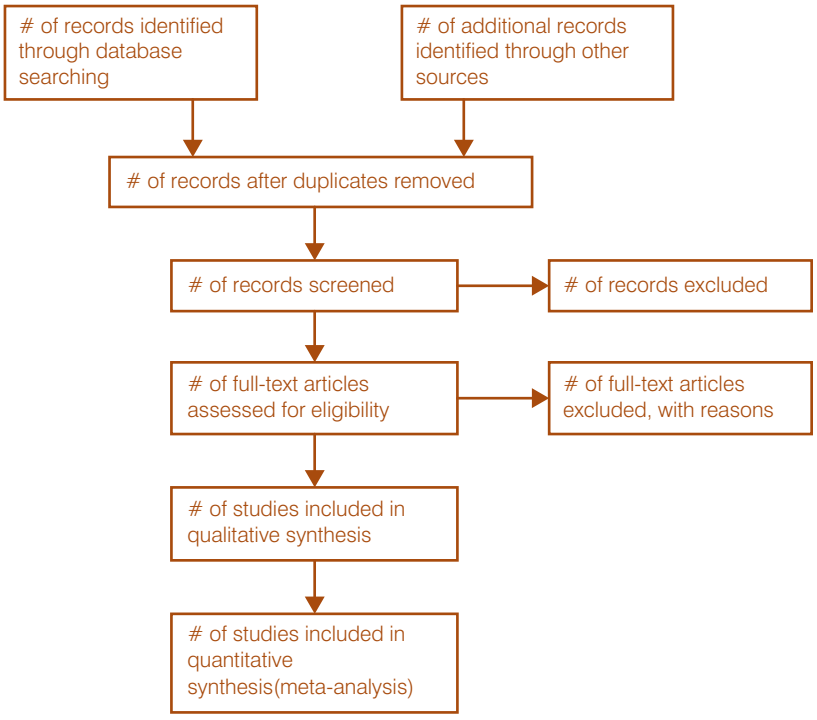

Figure 1 PRISMA Flow Diagram

Search and quality assessment for/of guidelines

Since the first meta-analysis was published in 1999[31], the electronic searches of PubMed were limited from the 1st of January 2000 to the 15th of August 2011. The following search terms were used: "pancreatitis AND (guideline OR guidelines OR practice guideline OR practice guidelines OR consensus)". The results were limited to articles published in the English, German and French language. Furthermore, only guidelines endorsed by a professional body and their latest updates were included. The Dutch guideline was added to the results although it is not indexed in PubMed[32].

The quality of the guidelines was assessed with the Grilli score[33] (Figure 2.) and AGREE (Appraisal of Guidelines for Research and Evaluation) Collaboration (http://www.agreetrust.org). The Grilli-score is an easy applicable quality assessment tool addressing 3 topic's: description of the involved professionals, description of the sources of information and explicit grading of evidence. The AGREE instrument provides a framework to assess the quality of guidelines by using 6 domains, with a total of 23 items. Every item can be scored, with a 1-7 point range. The domains

Description of the type of professionals involved in developing the guideline:		
Yes	If there was a description of the type of professionals and other stakeholders involved in the development process	2 points
Partially	If only a list of names with institutional affiliation was provided	1 point
No	If only names were reported, without further information	0 points
Description of the sources of information used to retrieve the relevant evidence:		
Yes	If it was explicitly stated that searches were undertaken, at least through MEDLINE	1 point
No	If no information was reported.	0 points
Explicit grading of the evidence in support of the main recommendations:		
Yes	If any form of explicit grading of the quality of the supporting evidence was reported	1 point
No	If otherwise	0 points

Figure 2 Checklist for quality assessment of guidelines endorsed by specialty societies

of AGREE are: scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence.

Statistical analysis

The 2010 journal impact factors were noted and quality assessment of the guidelines calculated by the Grilli-score (Box 1). The relation between the Grilli-score and impact factor was calculated with SPSS Pearson 2-tailed test (SPSS version 17).

RESULTS

Meta-analyses: ERCP versus conservative management of ABP

The initial PubMed search identified 24 articles for further review. Eight meta-analyses met the inclusion criteria and are presented in Table 1. Sixteen articles were excluded because they addressed other topics or were reviews. Impact factors ranged from 0.9 to 6.1. The number of included randomized trials varied from 2 to 5. Only 2 of 8 meta-analyses included the same studies.

Only the first meta-analysis concluded that an emergency ERCP/ES was beneficial in all patients with ABP (regardless of cholestasis/cholangitis), resulting in a significant reduction of morbidity and mortality ($p<0.001$ and $p<0.05$), particularly in predicted severe cases (Table 1)[31]. The remaining seven meta-analyses reported no beneficial effect of an emergency ERCP in patients with predicted mild ABP and did not specify the indication of an ES in predicted severe case.

In case of predicted severe ABP, the meta-analysis of Steinberg and Heinrich[34] concluded that an emergency ERCP ± ES resulted in a significant reduction of complications and mortality, but only in predicted severe cases of ABP (Table 1)[35]. The meta-analyses of Ayub[36] and Moretti[37] reported a significant reduction in morbidity but not mortality, in the emergency ERCP group with predicted severe ABP, regardless of cholestasis/ cholangitis (Table 1). Whereas the meta-analyses of Petrov[38], Uy[39], and Petrov[40] concluded that a an early ERCP in ABP was not associated with a significant reduction in morbidity and mortality in predicted severe cases (Table 1).

Guidelines: ERCP versus conservative management of ABP

The initial database search regarding "guidelines" identified 299 articles for further review. After reading the abstracts 22 potential guidelines were retrieved. Six papers were excluded because they lacked an official endorsement. Two older Japanese guidelines (2002[41] and 2006[42-44]) and one older Italian guideline[45] were excluded,

and were represented by the latest 2010 guidelines. The Dutch guideline was added to the search[64]. Two guidelines were excluded, because they did not mention a policy regarding the endoscopic treatment of ABP[46,47]. This resulted in 12 guidelines, which are reported in Table 2. The reported impact factor of the guidelines varied between not specified to 12.9. Regarding the quality of the guidelines, there was no significant correlation between the Grilli factor (0-3: low and 4: high quality) and AGREE-score versus the journal impact factor ($p=0.996$ and $p=0.573$). The Grilli factor was significant correlated to the AGREE-score ($R=0.762$, $p=0.004$).

Clinical trials and meta-analyses formed the basis of most guidelines (Table 2). However, guidelines of the Societé Nationale Française de Gastroenterologie[48] and American Gastroenterological Association[23] (AGA) did not report the references. All guidelines recommend an emergency ERCP in patients with ABP with co-existing cholangitis and/or biliary obstruction (Table 2). According to the included guidelines there is no indication for an emergency ERCP in patients with predicted mild ABP, without cholangitis and/or biliary obstruction. In case of a predicted severe ABP the guidelines are controversial.

The Japanese 2010 Guidelines[49 50-52] (Table 2) included the most clinical trials and meta-analyses and had a maximum Grilli score of 4. This is the only guideline that does not recommend an emergency ERCP in severe ABP. Four guidelines question the usefulness of an emergency ERCP in patients with predicted severe ABP: the French[48], International Association of Pancreatology[53], AGA, and Italian-guideline[54] (Table 2). The Grilli score of these guidelines varies between 2 and 4 and the number of studies (i.e., clinical trials or meta-analyses) that were included are low. Six guidelines recommend an emergency ERCP in patients with predicted severe ABP: the Dutch[64], Chinese[55], German[56], World Congress of Gastroenterology (WCG) [57], American thoracic society (ATS)[58], British[59], and American college of gastroenterology (ACG)-guidelines[60]. The optimal time period for ERCP differed among the guidelines: within 72 hours after onset of symptoms (WCG, ATS, British, Dutch) or within 24 hours after hospital admission (German and ACG).

The guidelines have several recommendations concerning the use of an early ES, whenever an early ERCP is performed. Six guidelines advise an ES, whenever emergency ERCP is performed (Table 2). In two guidelines an ES is advocated in case of biliary obstruction and/or cholangitis. (Table 2). However, the indication of an early ES is not specified in 4 guidelines.

Table 1 Meta-analyses on the use of routine emergency ERCP in acute biliary pancreatitis

	Impact factor journal	Studies included	Excluded studies	Reason exclusion
Meta-analysis 1 (Sharma et al, 1999)[31]	6.12	Neoptolemos[13] Fan[24], Nowak[25] Fölsch[23]	None	-
Meta-analysis 2 (Steinberg et al, 2001) [35].	2.61	Neoptolemos[13] Fan[24],	Nowak[25] Fölsch[23]	Abstract/ timing ERCP Excluding the non-biliary pancreatitis cases from the Hong Kong study[24].
Meta-analysis 3 (Ayub et al, 2004)[36]	5.65	Neoptolemos[13] Fan[24] Fölsch[23]	Nowak[25]	No conservative group
Meta-analysis 4 (Heinrich et al, 2006)[34]	7.9	Neoptolemos[13] Fan[24], Fölsch[23]	Nowak[25]	Abstract
Meta-analysis 5 (Petrov et al, 2008)[38]	7.9	Neoptolemos[13] Fölsch[23] Oria[26]	Fan[24] Nowak[25] Acosta[22]	ERCP in all acute pancreatitis No conservative group Treatment group: only 47% ERCP
Meta-analysis 6 (Moretti et al, 2008)[37]	2.97	Neoptolemos[13] Fan[24], Fölsch[23] Zhou[27], Oria[26]	Nowak[25] Acosta[22]	Abstract, different control group Different treatment group
Meta-analysis 7 (Petrov et al, 2008)[40]	3.31	Neoptolomos[13] Fan[24], Folsch[23] Oria[26],Acosta[22]	Nowak[25]	Abstract
Meta-analysis 8 (Uy et al, 2009)[39]	0.89 (estimated 2007)[71]	Fölsch[23] Oria[26]	Fan[24] Nowak[25] Zhou[27] Acosta[22] Neoptolomos[13]	All AP, cholangitis not excluded No information on cholangitis Did not exclude cholangitis. Excluded only severe cholangitis. Did not exclude cholangitis.

Abbreviations:
Ns not significant
N.S. Not specified

Morbidity (ERCP versus Conservative)	Mortality	ERCP in Mild ABP	ERCP in Severe ABP	ERCP in co-existent Cholangitis	Suspected Obstruction
Overall: 25.0% vs 38.2% (p<0.001)	Overall: 5.2% vs 9.1% (p<0.05)	Yes	Yes	Yes	Yes
Mild : 16% vs 16% (ns) Severe: 54% vs 15% (p<0.01)	Mild: 0% vs 0% (ns) Severe: 15% vs 2% (p<0.05)	No	Yes	Yes	N.S.
Mild ABP: OR=0.89 (ns) Severe ABP:OR=0.27 (95%CI 0.14-0.53)	Overall, mild and severe ABP (ns)	No	Yes	Yes	N.S.
Overall: 31.3% vs 41.8% (p=0.03) Mild ABP (ns) Severe ABP: 18.2% vs 57.1% (p<0.0001)	Mild ABP (ns) Severe ABP: 3.6% vs 17.9% (p=.0.03)	No	Yes	Yes	N.S.
Overall: ns Mild and severe ABP (ns)	Overall, mild and severe ABP (ns)	No	No	Excluded	N.S.
Overall: 27% vs 36% (p=0.01) Mild ABP (ns) Severe: rate difference 38.5% (p=<0.0001)	Overall, mild and severe ABP (ns)	No	Yes	N.S.	N.S.
Limited to local complications: Overall, mild and severe ABP (ns)	Overall, mild and severe ABP (ns)	No	No	N.S.	N.S.
Overall: ns Mild and severe ABP (ns)	Overall, mild and severe ABP (ns)	No	No	Excluded	N.S.

Table 2 Guidelines addressing the use of routine emergency ERCP/ES in acute biliary pancreatitis

Guidelines	Year	Impact factor journal	Grilli Score	AGREE	Studies/ Meta-analysis
Societé Nationale Française de Gastroenterologie[48] (French)	2001	1.7	2	51	N.S.
International Association of Pancreatology[53] (IAP)	2002	1.4	3	76	Neoptolomos, Fan, Folsch
World Congress of Gastroenterology[57] (WCG)	2002	2.3	3	65	Neoptolomos, Fan, Nowak, Folsch
Chinese society of Gastroenterology[55]	2004	1.6	0	23	N.S.
American Thoracic Society[58] (ATS)	2004	6.4	4	69	Neoptolomos, Fan, Nowak, Folsch, Sharma
British Society of Gastroenterology[59] (British)	2005	9.4	3	84	Neoptolomos, Fan, Folsch, Nowak
Dutch Society of Internal Medicine[32] (Dutch)	2005	N.S.	4	80	Neoptolomos, Fan, Nowak, Folsch
American College of Gastroenterology[60] (ACG)	2006	6.1	4	73	Neoptolomos, Fan, Nowak, Folsch, Sharma, Ayub
American Gastroenterological Association[23] (AGA)	2007	12.9	2	70	N.S.
German Society for Digestive Diseases and Metabolic Diseases[56] (German)	2007	1.2	4	85	Neoptolomos, Fan, Folsch, Oria, Ayub
Italian Association for the Study of the Pancreas[54] (Italian)	2010	3.0	4	54	Petrov, Moretti
Japanese Guidelines[49] [50-52]	2010	1.9	4	82	Neoptolomos, Fan, Nowak, Folsch, Zhou, Acosta, Oria, Sharma, Ayub, Heinrich

Mild biliary pancreatitis	Severe biliary pancreatitis	Cholangitis	ERCP advised in Suspected Obstruction	Endoscopic Sphincterotomy
No	Debate	Yes	Yes	When ERCP is indicated
No	Debate	Yes	Yes	When ERCP is indicated
No	Yes	Yes	Yes	When ERCP is indicated
No	Yes	Yes	Yes	When ERCP is indicated
No	<72h onset symptoms	Yes	Yes	N.S
No	<72h onset symptoms	Yes	Yes	When ERCP is indicated
-	< 72h (N.S.)	Yes (<24h)	Yes (<24h)	Obstruction Cholangitis, CBDS
	<24h admission	Yes	Elective ERCP in persistent obstruction	N.S.
No	controversial	Yes (<24h)	Yes (<72h)	N.S.
No	Yes (<24h Admission)	Yes (<24h)	Yes (<24h)	Cholangitis, Jaundice, Cholestasis
No	controversial	Yes	Yes	When ERCP is indicated
No	No	Yes	Yes	N.S.

DISCUSSION

At present, according to published meta-analyses and national guidelines, two statements about early ERCP/ES in ABP seem un-debated: 1. ERCP/ES does not have a clear advantage in patients with predicted mild ABP and 2. co-existing cholangitis is an indication for emergency ERCP/ES (within 24 hours of admission). However, consensus is lacking on the role of routine early ERCP/ES in all patients with predicted severe ABP, regardless of cholestasis.

How is it possible that meta-analyses on the same subject reach such different conclusions? There are two likely explanations for this to happen. The first possible explanation is time of publication. More recent meta-analyses or guidelines might reach different conclusions as new data has come available over time. However, this argument is contradicted by the observation that the latest meta-analyses (2006-2009: Table 1) are not concurrent in which of the most recent (randomized) clinical trials were included in their analysis: Acosta[22](2006), Oria[26](2007) and van Santvoort[61] (2009), which results in conflicting outcomes (like the older meta-analyses). The second likely explanation is what has just been alluded to that is selection of which studies to include in the meta-analysis. For example, in contrast to all other meta-analyses only Sharma et al[31] included the study of Nowak et al[25], although only published in abstract. This already provides ample explanation why only this meta-analysis recommends early ERCP in predicted mild ABP. For the use of ERCP in predicted severe cases of ABP the outcome of the 8 meta-analyses depend on the in[27,34,36,62] or exclusion[38,39], of the study of Neoptolomos[13] and/or Fan et al[24].

In the light of contradictory recommendations of clinical trials, meta-analyses and guidelines we recently surveyed the daily clinical practice among Dutch gastroenterologists[63]. Of the 97% responders who would consider performing an early (<72h) ERCP in ABP, 14% stated that they always perform ERCP regardless of the presence of any condition or symptom. The remainder of the respondents considers ERCP only if a concomitant condition is present such as a dilated CBD (95%), co-existent cholangitis (87%), common bile duct stone(s) (CBDS) (72%), jaundice (59%), ampullary stone (68%) or (predicted) severe-ABP (35%). Accordingly, the study of Van Santvoort et al. demonstrated that in daily clinical practice in the Netherlands the use of ERCP in predicted severe ABP varied from 0 to 100% in 15 of the largest Dutch hospitals[64]. Similar defiance of the national guidelines were reported in an Italian and British surveys.[65-67] In a British survey amongst surgeons (n=583), 35% advocated early ERCP /ES in patients with predicted severe biliary pancreatitis and a further 14% ERCP/ES for all patients with biliary pancreatitis regardless of the predicted severity[68].

Interestingly, apart from the first meta-analysis, none specified the indication for early ES in patients with ABP. Furthermore, the indication for ES is also not specified in the American and Japanese guidelines. Literature concerning this topic is remarkably scarce. Only one randomized clinical trial addressed this issue and reported a significantly decreased morbidity and mortality in patients with an early ERCP with ES compared to ERCP alone[25]. These results were partly confirmed by an univariate analysis in a prospective clinical trial of Van Santvoort et al[61]. In this study, ES was associated with a significant reduction in overall complication rate (adjusted OR 0.24; 95% CI 0.06-0.93; $P = 0.04$) albeit without a significant effect on mortality (adjusted OR 1.38; 95% CI 0.13-14.44; $P = 0.79$).

The present systematic review clearly demonstrates that despite numerous randomized trials, there is an obvious lack of consensus on the indications, the timing, and procedural techniques (ES or not) in meta-analyses and nationwide guidelines. Three strategies might possibly improve consensus. First, uniform criteria for inclusion of studies in meta-analyses and guidelines would increase the likelihood of reaching consensus. Future versions of the PRISMA guidelines for systematic reviews and meta-analyses could provide such criteria. Second, rather than performing meta-analyses of literature reports, future meta-analyses should aim to aggregate and analyze individual patient data. It has been shown that individual patient data meta-analyses (IPDMA) provide more reliable outcomes than regular meta-analyses[69]. Third, an obvious strategy would be to perform new high quality randomized trials on relevant questions reflecting patient management in daily clinical practice, for example about the role of (early) ERCP in patients with predicted severe acute biliary pancreatitis. Such a study should be adequately powered, using practical inclusion criteria, clear crossing-over criteria, a cannulation failure scenario, and end-points that are clinical relevant in terms of patient outcome. ES should be an integral part of ERCP treatment[70]. The preparation of such a trial has started and will be carried out by the Dutch Pancreatitis Study Group. In this APEC-trial (Acute biliary Pancreatitis: early ERC plus ES versus Conservative treatment: APEC), a randomized, superiority, assessor-blinded multicenter trial, patients with ABP are randomized within 24h admission between a conservative and ERC/ ES group.

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CHAPTER 3

ENDOSCOPIC TREATMENT OF ACUTE BILIARY PANCREATITIS: A NATIONAL SURVEY AMONG DUTCH GASTROENTEROLOGISTS

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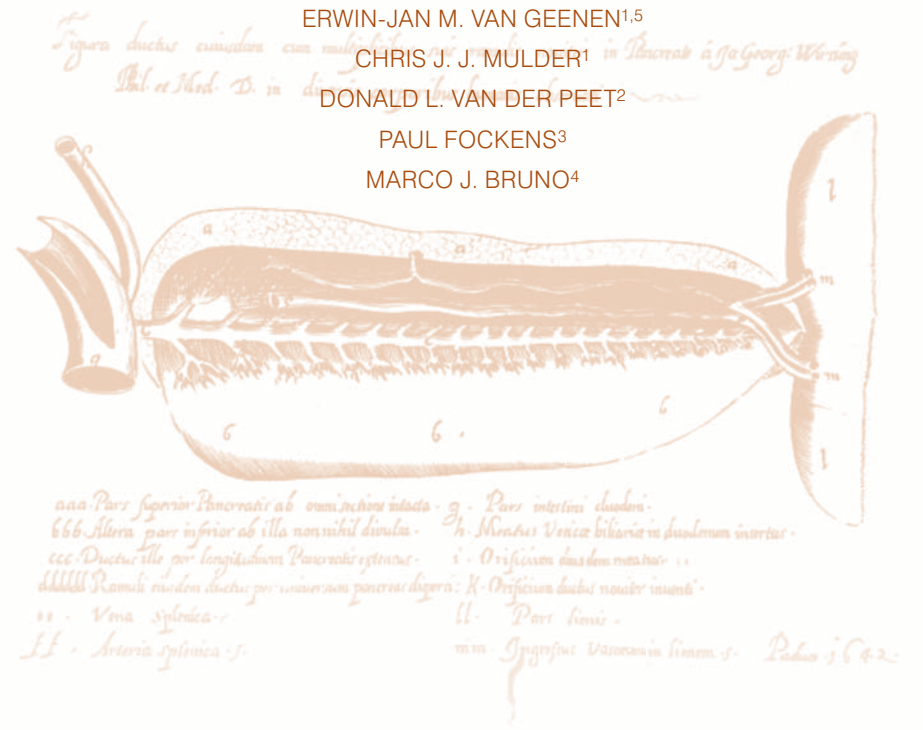

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ABSTRACT

Objective. Based on the ampullary obstruction and reflux theory, six endoscopic retrograde cholangiopancreatography (ERCP) studies have investigated the effect of (early) biliary decompression versus conservative management on the course and outcome of patients with acute biliary pancreatitis (ABP) showing inconsistent and contradictory outcomes. We investigated the opinion and attitude of Dutch gastroenterologists regarding the application of (early) ERCP in the clinical management of ABP by means of a nationwide survey.

Material and methods. An anonymous questionnaire was sent to all registered consultant gastroenterologists (n = 283) across the Netherlands. Results. The response rate was 52%. The vast majority of consulting gastroenterologists declared that early ERCP may be indicated in ABP (96.6%). Fourteen percent stated that they always perform ERCP in ABP. The remainder of the respondents consider ERCP only if a concomitant condition is present such as a dilated CBD (95%), co-existent cholangitis (87%), common bile duct stone(s) (CBDS) (72%), jaundice (59%), ampullary stone (68%) or (predicted) severe ABP (35%). About half of the consultant gastroenterologists (51.4%) consider the optimal time point for ERCP in ABP to be within 24 h after admission or symptom onset. If ERCP is performed for suspected APB, 55% of the respondents perform an endoscopic sphincterotomy (ES), regardless of the findings on cholangiography.

Conclusions. The vast majority of Dutch gastroenterologists attest to a role for ERCP in ABP, but indications when to perform ERCP, its timing, and the application of ES vary greatly and are not always in line with the Dutch or other published national guidelines. The results of this survey highlight the need for additional comparative randomized studies to define the role of (early) ERCP in ABP.

INTRODUCTION

Gallstones account for 35–60% of acute pancreatitis cases in the United States and Western Europe [1–3]. Approximately 25% of patients develop severe acute biliary pancreatitis (ABP) including necrotizing pancreatitis and multiple organ failure. The overall mortality ranges between 2 and 10% [1,2]. The incidence of ABP has increased during the last decade by 35% in the western countries [4]. Several theories have been put forward about the etiology of ABP including ampullary obstruction, (infected) bile reflux into the pancreatic duct, and an increase in pancreatic enzyme production/activation by duodenal bile exclusion [5–10]. Based on the ampullary obstruction and reflux theory of Opie and Bernard, two surgical trials [11,12] and six prospective randomized endoscopic retrograde cholangiopancreatography (ERCP) studies have investigated the effect of (early) biliary decompression versus conservative management on the course and outcome of patients with ABP [13–18]. These studies form the basis for several meta-analyses and national guidelines. The first meta-analysis (1999, n = 834) recommended ERCP and endoscopic sphincterotomy (ES) in all patients with ABP, particularly in predicted severe cases [19]. The second meta-analysis (2004, n = 511) made a clear distinction between patients with and without acute cholangitis and showed that early ERCP decreases complications in all patients with predicted severe ABP [20]. The third meta-analysis (2008, n = 450) [21] that included the new Argentinean study [18] indicated that ERCP in patients with both predicted mild and severe ABP without cholangitis does not lead to a significant reduction of overall complications and mortality. The UK guideline (2005) states that all patients with predicted severe ABP should undergo early ERCP [22]. The American Gastroenterology Association (2007) states that early ERCP in predicted severe ABP without signs of cholangitis is controversial [23] and the American College of Gastroenterology (2006) recommends that early ERCP is to be performed only in patients with severe ABP and acute cholangitis [24]. The Japanese guidelines (2006) recommend an urgent ERCP in patients in whom biliary duct obstruction is suspected and in patients with cholangitis [25]. The Dutch guidelines published by the Dutch internal medicine association (2005) state that ERCP is warranted within 24 h in patients with predicted severe ABP with cholangitis or biliary obstruction and within 72 h in cases with predicted severe ABP without signs of cholangitis or obstruction [26]. All guidelines state that an emergency ERCP in predicted mild ABP is not indicated. In the light of the somewhat confusing and in part conflicting recommendations we investigated the opinion and attitude of Dutch gastroenterologists toward the application of (early) ERCP in the clinical management of ABP by means of a nationwide survey.

METHODS

A questionnaire was sent by mail to all registered gastroenterologists across the whole of the Netherlands in May 2008 (registry source: Dutch Association of Gastroenterologists). In total 283 consultant gastroenterologists were invited to participate in this anonymous survey. The questionnaire consisted of nine questions. Five questions dealt with demographic issues including age, gender, type of hospital (academic, community hospital), total years of ERCP experience, and number of ERCPs performed yearly. The remaining questions focused on the endoscopic management of ABP: Is there an indication for early ERCP (multiple conditions listed, more than one could be selected)? In what time frame in relation

Table 1 Questionnaire

1. Function	Gastroenterologist Other
2. Age	……years
3. Gender	M / W
4. Hospital	General / academic
5. ERCP's/year and years of experience	
6. Indication for early ERCP in ABP (< 24 till 72 hours after admission)	Yes No: Not enough evidence/ experience/ expert based/ I don't no
7. When is an early ERCP indicated	a. Always b. Cholangitis c. Predicted severe pancreatitis:…….. d. Increased bilirubine:……..uM e. Common bile duct (CBD)stones f. Distended CBD……mm (age, CC) g. Papillary stone h. other reason;……..
8. When do you perform an ERCP in ABP?	a. < 24h after onset symptoms / admission b. <48h after onset symptoms / admission c. < 72h after onset symptoms / admission d. Other timing:…….
9. When do you perform an endoscopic sphincterotomy (ES), when an ERCP is carried out	a. Always b. CBD stones (CBDS) c. Distended CBD on cholangiography d. Ampullary stone e. Increased bilirubine without CBDS f. Cholangitis g. Other;…….

to start of symptoms or admission is an early ERCP indicated (within 24, 48, or 72 h)?; when is an early ERCP indicated? (multiple conditions listed, more than one could be selected); in what circumstances/ conditions do you perform a sphincterotomy? (multiple conditions listed, more than one could be selected). Questions had additional space for free text (Table I). Closure date for receiving the questionnaires was August 2008. Descriptive statistics were applied to summarize results.

RESULTS

Two hundred eighty-three questionnaires were sent to consultant gastroenterologists and responses were received from 148, a response rate of 52%.

Characteristics of responders

Eighty-three percent of the responders were men, with an average age of 47 years (SD 8). Twentythree percent were employed in an academic hospital. The vast majority (92%) performed ERCP in daily practice, with an average practice time of nearly 12 years and an average of 70 ERCP yearly.

Indication for ERCP

The vast majority of gastroenterologists (n = 144, 96.6%) stated that they would considerer performing early ERCP, within 72 h of admission, in patients with suspected ABP. Of these 144 gastroenterologists, only 10 did not routinely perform ERCPs as they did not master this technique themselves. Four gastroenterologists disapproved of any indication for early ERCP in ABP, three because of insufficient scientific evidence to support its application and one based on “gut-feeling”. Of the 96.6% responders who would consider performing ERCP in ABP, 14% stated that they always perform ERCP. The remainder of the respondents considers ERCP only if a concomitant condition is present such as a dilated CBD (95%), coexistent cholangitis (87%), common bile duct stone (s) (CBDS) (72%), jaundice (59%), ampullary stone (68%) or (predicted) severe ABP (35%).

Timing of ERCP

More than half of the consultant gastroenterologists (51.4%) consider the optimal time point to perform ERCP in ABP to within 24h of admission or after first symptoms (Table II).Timing of ERCP within 48 h after admission or start of symptoms was still considered appropriateby72.3%ofgastroenterologists.The timing in 6.1% was determined by clinical signs of the patient with ABP. The mean age of responders did not differ between the different time intervals (data not shown). Application of endoscopic sphincterotomy Fifty-eight percent of the consultant gastroenterolo-

gists always perform an ES whenever they carry out an ERCP for suspected ABP, regardless of the presence or absence of specific features. The percentage of responders who would perform ES in the presence of a particular feature was: CBDS 98%, distended CBD 77%, cholangitis 75%, ampullary stone 76.5%, and increased bilirubin 41%.

Table 2 Timing of ERCP

Timing of ERCP(N = 148)		*Cumulative*
< 24h after first complaints	(9) 6.1%	
< 24h after admission	(29) 19.6%	
< 24h after first complaints or admission	(34) 23%	
< 24h after first complaints or admission: in SABP	(4) 2.7%	51.4%
< 48h after first complaints	(13) 8.8%	
< 48h after admission	(6) 4.0%	
< 48h after first complaints or admission	(12) 8.1%	72.3%
< 72h after first complaints	(18) 12.1%	
< 72h after admission	(2) 1.3%	
< 72h after first complaints or admission	(10) 6.8%	89.1%
Depending on clinical sign's	(9) 6.1%	98.6
Never	(2) 1.4%	100%

DISCUSSION

The response rate of our nationwide questionnaire was 52%, which is well in line with other surveys [27–29]. With 92% of responders performing ERCPs, with an average procedural experience of 11.7 years and an average yearly case load of 70 procedures, this survey gives an interesting insight into the opinion and attitude of experienced endoscopists with regard to the indication of ERCP in suspected ABP in the Netherlands. Several guidelines exist with regard to the endoscopic treatment in suspected ABP (Table III). These guidelines are based on conflicting data from a few clinical randomized trials comparing ERCP with or without ES with conservative management in ABP [13–16,18,30] and have non-uniform outcomes and recommendations (Table III). Nevertheless, two statements about early ERCP in APB seem undebated at present: (1) ERCP does not seem to have a clear advantage in patients with predicted mild ABP and (2) co-existing cholangitis is an indication for

an emergency ERCP (within 24 h of admission). The aim of the present study was to assess the opinion and attitude of Dutch gastroenterologists on early ERCP in ABP compared with published studies and national guidelines. The vast majority of consultant gastroenterologists (96.6%) attest to a potential role for (early) ERCP in ABP. In this regard it should be noted that in the Netherlands, like in most parts of Europe, ERCPs are carried out by gastroenterologists. In the United Kingdom, however, many surgeons perform ERCP. It would be interesting to know whether their opinions differ from those of gastroenterologists. Seven percent of Dutch gastroenterologists claim that ERCP is always indicated in ABP, regardless of the presence or absence of any additional sign or symptom. This would indicate that those colleagues also perform ERCP in uncomplicated cases without a predicted severe disease course. In line with the outcome of the meta-analyses and the majority of published guidelines, the vast majority of responders (87%) consider ERCP a legitimate procedure in case of cholangitis. Thirteen percent does not recognize the potential benefits of early ERCP in case of cholangitis and probably rely on antibiotics, judging against all guidelines. Remarkably, a predicted course of severe AP was a reason to perform an ERCP for only 35% of responders, which is in sharp contrast to the national Dutch, US, and UK guidelines. These results might be explained by the lack of guideline knowledge, a disbelief in the guidelines, or the impact of the recent meta-analysis of Petrov et al. [21], which indicates hat ERCP in patients ABP without cholangitis does not lead to a significant reduction of overall complications and mortality. In case of suspected or proven biliary obstruction depending on which additional sign or symptom is present including jaundice, dilated CBD, CBDS, or ampullary stones, 60–95% of the responders perform an ERCP in ABP. This is in line with Dutch and Japanese guidelines. However, only for a dilated CBD there is near consensus with 95% of responders performing ERCP. In case of jaundice, CBDS, or an ampullary stone less than two-thirds of responders consider ERCP. The small majority of responders (54%) perform ERCP within 24 h after the onset of symptoms or hospital admission. This is in accordance with the Dutch guidelines in patients with predicted severe ABP with cholangitis or biliary obstruction. The remainder still performs ERCP within 72 h, which in accordance to the guidelines would be appropriate in cases with predicted severe ABP without signs of cholangitis. Nearly 60% of endoscopists always perform an ES in case of suspected ABP. Ninety-eight percent performs an ES whenever CBDS are detected. Other indications to carry out an ES range from 40 to 77%, indicating a liberal application, but not uniform consensus in the application of ES. Importantly, studies have not systematically addressed this important aspect of ERCP in ABP. National guidelines do not specify if and when an ES should be performed. This survey reflects the current opinion of Dutch gastroenterologists regarding the application of early ERCP in ABP in the Netherlands

and to what extent ollowed. There is no apparent reason to assume that in other European countries in which primarily gastroenterologists perform ERCP, results would be different. Despite published studies and national guidelines, the indications to perform ERCP and its timing vary greatly. There is also no uniformity as to if and when ES is done. One could argue if this is due to ignorance about studies results and published guidelines. However, in recent years substantial attention has been drawn to this issue, especially in relation to the recently published Dutch guidelines. It therefore seems more likely that many Dutch endoscopists are not convinced by the existing literature evidence and proposed guidelines and still follow their "gut" feeling. The results of this survey highlight the need for additional clinical trials. For such studies to have a true impact on practicing physicians, they should reflect patient management in daily clinical practice. This would require a comparative trial with a sufficient number of patients using practical inclusion criteria, clear crossing-over criteria, a cannulation failure scenario, and end-points that are clinically relevant in terms of patient outcome. In such a study ES should be an integral part of ERCP treatment.

Table 3 Indication of ERCP in treatment of ABP: the guidelines and meta-analysis

National guideline/meta-analysis	Mild	Severe	Cholangitis	Suspected Obstruction
UK[22]	-	+	+	-
USA / AGA[23]	-	+/-	+	-
USA / ACG[24]	-	+	+	-
Japan[25]	-	-	+	+
Netherlands[26]	-	+	+	+
Meta-analysis 1 (Sharma et al, 1999)[19]	+	+	+	+
Meta-analysis 2 (Ayub et al, 2004)[20]	-	+	+	-
Meta-analysis 3 (Petrov et al, 2008)[21]	-	-	+	-

UK United Kingdom
AGA American Gastro Association
ACG American College of Gastroenterologists

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CHAPTER 4

RECURRENT ACUTE BILIARY PANCREATITIS: THE PROTECTIVE ROLE OF CHOLECYSTECTOMY AND ENDOSCOPIC SPHINCTEROTOMY

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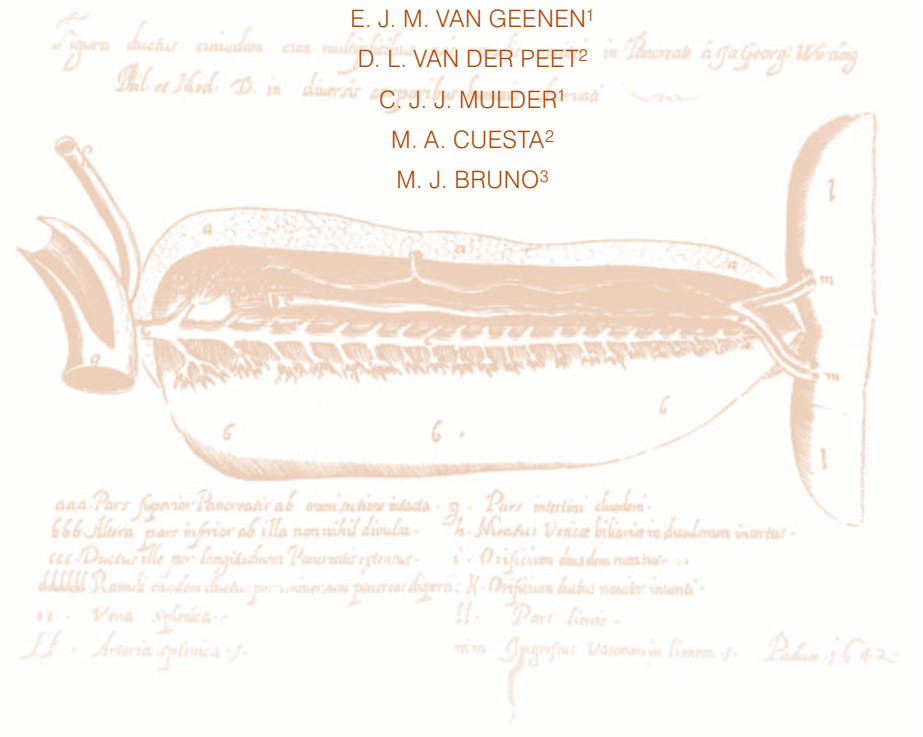

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ABSTRACT

Background. Recurrent attacks of acute biliary pancreatitis (RABP) are prevented by (laparoscopic) cholecystectomy. Since the introduction of endoscopic retrograde cholangiopancreaticography (ERCP), several series have described a similar reduction of RABP after endoscopic sphincterotomy (ES). This report discusses the different treatment options for preventing RABP including conservative treatment, cholecystectomy, ES, and combinations of these options as well as their respective timing.

Methods. A search in PubMed for observational studies and clinical (comparative) trials published in the English language was performed on the subject of recurrent acute biliary pancreatitis and other gallstone complications after an initial attack of acute pancreatitis.

Result. Cholecystectomy and ES both are superior to conservative treatment in reducing the incidence of RABP. Cholecystectomy provides additional protection for gallstone- related complications and mortality. Observational studies indicate that cholecystectomy combined with ES is the most effective treatment for reducing the incidence of RABP attacks.

Conclusion. From the literature data it can be concluded that ES is as effective in reducing RABP as cholecystectomy but inferior in reducing mortality and overall morbidity. The combination of ES and cholecystectomy seems superior to either of the treatment methods alone. A prospective randomized clinical trial comparing ES plus cholecystectomy with cholecystectomy alone is needed.

INTRODUCTION

Acute biliary or gallstone pancreatitis (ABP) is an inflammatory condition of the pancreas induced by gallstones [1]. The initial treatment of ABP can be either conservative or interventional. The coexistence of cholangitis is an accepted indication for the performance of endoscopic retrograde cholangiopancreaticography (ERCP). However, whether this procedure is performed for patients with ABP depends on local expertise and guidelines, as is the decision to perform an endoscopic sphincterotomy (ES) [2–5]. After patients have recovered from their first attack of ABP, most guidelines advocate a cholecystectomy to prevent a recurrent attack or other gallstone-related disorders such as symptomatic choledocholithiasis, cholecystitis, gallstone ileus, jaundice, and cholangitis [2–5]. ''Recurrent'' symptomatic choledocholithiasis after an initial attack of ABP may be preexisting common bile duct (CBD) stones not detected at the time of the primo episode or stones that migrated from the gallbladder into the CBD after initial stone clearance. Choledocholithiasis also may have developed newly within the bile duct after cholecystectomy. The incidence of recurrent acute biliary pancreatitis varies widely, from 0% to 57%, depending on the population studied, the initial treatment, and the follow-up time (Table 1). Recently, observational studies point toward a reduction in recurrent ABP attacks and other gallstone complications when ES is performed for selected groups of patients [6–10]. Based on whether a patient has undergone ES, cholecystectomy, or both, the post-ABP-status of a patient can be classified into four categories: 1 (no ES and no cholecystectomy), 2 (no ES with cholecystectomy), 3 (ES without cholecystectomy), or 4 (ES with cholecystectomy). To date, no studies have compared any combination of these conditions (Table 1). The current report reviews additional medical interventions to determine which are most effective for preventing recurrent medical problems after an attack of ABP.

Cholecystectomy versus conservative treatment

Evidence that a cholecystectomy actually reduces the incidence of recurrent ABP is scarce. The evidence that does exist originates mainly from older retrospective studies that observed no recurrent ABP after a cholecystectomy compared with a 25% to 61% rate of ABP recurrence with conservative management [11–17]. From a retrospective population-based cohort study, it was concluded that a cholecystectomy reduces the risk of a recurrent or de novo ABP almost to the same level as found in the general population [18]. The overall age- and sex-adjusted incidence of acute pancreatitis before cholecystectomy was 6.3 to 14.8 per 1,000 patient years. Cholecystectomy for patients without a prior ABP attack reduced the relative risk for the development of acute pancreatitis to 2 (0.65 per 1,000 person years). The recurrence rate for acute pancreatitis of cholecystectomized patients was 2.7

Table 1 Recurrent Acute Biliary Pancreatitis (ABP)

Study [a]	Recurrent ABP % (n)	Recurrent ABP after ES % (n)	Recurrent ABP after cholecystectomy % (n)	Recurrent ABP after cholecystectomy and ES % (n)
Kaw, Billi, Hammarstrom, Vazquez-Lglesias, Gislason [7, 8, 22–24]		0.9–6.4		
Uomo [6]	57 (7)	5 (19)		
Kaw [7]		2.9 (34)	2.4 (83)	
Billi [22]		6.4 (47)		
Hammarstrom [8]	12.5 (16)	2 (49)	19 (16)	0 (15)
Vazquez-Iglesias [23] Paloyan [21] Kahaleh [79]	48 (64)	2.2 (88) 2.1 (96)		3.0 (66)

ES endoscopic sphincterotomy

[a] All studies are prospective, observational, and non-randomized

per 1,000 patient years. However, none of these had a biliary origin. Importantly, 13% to 14% of all patients presenting with ABP have a history of a prior cholecystectomy without having undergone ERCP and ES [19, 20].

Endoscopic sphincterotomy versus conservative management

Uomo et al. [6] prospectively investigated the effect of ES on patients after a first attack of ABP who were considered unfit for surgery. In the ES group, the observed rate of recurrent ABP was 5% compared with 57% in the conservative group after a mean follow-up period of 30 and 23.8 months, respectively. Paloyan et al. [21] confirmed this rate of ABP recurrence after conservative treatment with their rate of 48%. However, Hammarstrom et al. [8] observed a 12.5% rate of ABP recurrence in noncholecystectomized patients during a median follow-up period of 79 months. Other prospective observational studies with various follow-up times showed ABP recurrence rates of 0.9% to 6.4% for patients treated with ES alone [7, 8, 22–24]. Intraoperative choledocholithiasis is present in 13% to 24% of patients undergoing cholecystectomy and bile duct exploration for symptomatic gallstone disease [25–29], including ABP [29, 30]. In 3% to 6% of the patients in whom CBD stones were detected, the stones were asymptomatic without preoperative indicators, negative abdominal ultrasound findings, or laboratory parameters [25, 29, 31]. It is believed that about 15% of these asymptomatic patients eventually will become symptomatic and require further interventional treatment [32]. Evaluation of the CBD for a planned cholecystectomy to decide on CBD exploration should be scheduled with a tight interval because the prevalence of CBD stones may change in time. In fact, multiple studies have shown that the prevalence of CBD stones in relation to admission time decreases because of spontaneous stone migration [33–37] (Table 2). Conversely, when a CBD is found to be free of stones at admission, this might be not representative for the time of surgery because migration of gallbladder stones into the CBD may have occurred just before the operation. From a clinical management point of view, patients referred to the surgeon for a laparoscopic cholecystectomy after an attack of ABP can be classified as follows according to what is known about the presence of CBD stones: 1 (cleared CBD after ERCP/ES), 2 (no CBD stones on previous imaging investigations including ultrasound, magnetic resonance cholangiopancreatography [MRCP], endoscopic ultrasound [EUS], and ERCP), or 3 (unknown CBD stone status). Hence, perioperative CBD stone clearance is of great importance. Clayton et al. [38] performed a meta-analysis to compare endoscopic removal of CBD stones and cholecystectomy with cholecystectomy and intraoperative removal of CBD stones in terms of morbidity and mortality. They concluded that both approaches had similar outcomes and that treatment should be determined by local resources and expertise. Laparoscopic CBD duct exploration seems to be an ideal approach, but

most surgeons still are uncomfortable and untrained with this technique. The potential drawback of finding CBD stones intra-operatively is that conversion to an open procedure sacrifices the advantage of the laparoscopic approach. However, a postoperative ERCP may be unsuccessful in clearing the CBD, necessitating a second surgical procedure. Adopting a wait-and-see policy is associated with additional interventions and increased morbidity [32, 39–41]. On the other hand, a ''diagnostic'' ERCP for detection and potential clearance of CBD stones before surgery is not justified because 76% to 87% of patients have no CBD stones, and the costs and potential complications of such an invasive approach are considerable [25–29].

Table 2 Incidence of common bile duct (CBD) stones in acute biliary pancreatitis (ABP) in relation to time [33–37]

Time from admission	CBD stones (%)
Admission	50-70%
< 24h	27
< 48h	23.1
2-3 days	25
4-5 days	12.5
>7 days	8

ACG American College of Gastroenterologists

In light of these considerations, preoperative assessment of CBD stones by means of noninvasive and cost-effective procedures such as laboratory values, multi-item scores, and imaging methods is of great clinical relevance. A wide variety of multi-item scores are suggested to be useful, but no two studies have identified the same variables. Factors thought to be discriminative by some are found to be of little use by others [41–63]. Recently, two studies assessed the value of gammaglutamyl- transferase (gGT) as a potential predictor for the presence of CBD stones. Peng et al. [64] investigated patients presenting with cholecystitis and found that there was a 33% chance of concomitant CBD stones with a gGT higher than 90 U/l and less than a 2% chance with a gGT lower than 90 U/l. In 1,002 patients undergoing laparoscopic cholecystectomy for any reason, Yang et al. [65] observed that abnormal gGT values had a sensitivity of 84.1%, a specificity of 72%, a positive predictive value of 22.4%, and a negative predictive value of 97.9% for detecting concomitant CBD stones before surgery. Radiologic imaging techniques also can be used to detect CBD stones. Abdominal ultrasound is the safest,

cheapest, and least invasive imaging method available for visualizing the biliary tree. Unfortunately, its performance in detecting CBD stones is disappointing, with a reported sensitivity of only 25% to 58% and a specificity of 68% to 91% [66]. The sensitivity of the CT scan for detecting CBD stones is about 40%, which is too low for it to be of clinical use [67]. However, MRCP is a very accurate method detecting CBD stones, with a reported sensitivity of 82% to 95%, a specificity of 97.5% to100%, a positive predictive value of 95% to100%, and a negative predictive value of 90% to 98% [33, 68–73]. In a systematic review of seven prospective trails, Ledro- Cano [74] compared the performance between MRCP (n = 411) and endoscopic ultrasonography (n = 411) in detecting choledocholithiasis. They concluded that both imaging methods had a comparable and very high accuracy in detecting CBD stones. Some individual studies suggest that MRCP has a slightly lower sensitivity for detecting stones than EUS because the sensitivity of MRCP decreases as follows when stones become smaller: 67% to 100% for stones larger than 10 mm, 89% to 94% for stones measuring 6 to 100 mm, and 33% to 71% for CBD stones smaller than 6 mm [69–72] Endoscopic sphincterotomy and cholecystectomy Hammarstrom et al. [8] followed 96 patients after an initial ABP event in an observational non randomized study for a median of 79 months (range, 33–168 months). From this potentially biased study, it was concluded that ES without a cholecystectomy reduced the overall incidence of recurrent pancreatitis event (4.7% vs 9.4%; p = 0.02). Of those patients initially treated using ES, 35% required an additional cholecystectomy during the follow-up period. It is reported that 2% to 33% of patients with symptomatic choledocholithiasis require an additional cholecystectomy, suggesting that patients with ABP are at greater risk for late gallstone-related complications [75– 77]. This also is supported by the observation that 15% of the patients from the Hammarstrom study required an emergency cholecystectomy after ES, compared with only 4% to 6% of patients presenting with symptomatic gallstone disease but not ABP [8, 75]. Higher cholecystectomy rates probably are due to the risk of acute cholecystitis after ES, which alone does not have a clear etiology [8, 78]. In a prospective non- randomized trial, Kahaleh et al. [79] investigated the rate of ABP recurrence after ES (n = 96) compared with ES and cholecystectomy (n = 66). The mean follow-up period was 1091 days. The observed rate of ABP recurrence was 2.1% compared with 3% (p = 0.278). Evidently, because of the nonrandomized study design, selection bias cannot be ruled out. Furthermore, this study has been published only in abstract form and other recurrent gallstone complications, for example, are not discussed. From the literature, the picture emerges that ES reduces the number of recurrent ABP events more than a cholecystectomy. Does this mean that we can skip performing a cholecystectomy after ABP? The answer is not straightforward. McAlister et al. performed a meta-analysis that included five prospective randomized trials [9, 80–83] showing the benefit of

an additional cholecystectomy after ES in case of symptomatic gallstone diseases, including ABP [84]. An additional cholecystectomy resulted in a lower death rate (7.9% vs 14.1%; p = 0.01) even in studies that included patients from higher-risk American Society of Anesthesiology (ASA) classes. In the patients for whom a wait-and-see policy was adopted, 16% experienced the development of biliary type pain or cholecystitis (relative risk [RR], 14.56; confidence interval [CI], 4.95–42.78), and more patients experienced recurrent jaundice or cholangitis (RR, 2.53; CI, 1.09–5.87; p = 0.03), but no significant difference in recurrent ABP rates was observed (0.3% vs 1.3%; p = 0.39). Eventually, for 35% of the patients subjected to a wait-and-see policy, an additional cholecystectomy was performed, with median follow-up times ranging from 30 to 80 months. From these data, it seems apparent that a cholecystectomy after an ABP event is beneficial and indicated. What about the timing of the operation? No scientific data exist to guide the timing of surgery. Expert opinion guidelines are based on sound and practical reasoning. Windsor [17] proposed that a cholecystectomy should be performed within 1 month after the first episode of ABP because most recurrent ABP events occur within 1 month (if no additional ES was performed). When the initial episode of ABP is severe and accompanied by peripancreatic fluid collections or pseudocysts, cholecystectomy should be delayed until the pseudocysts have either resolved or persisted beyond 6 weeks, at which time pseudocyst drainage can safely be combined with cholecystectomy [85]. Hammarstrom et al. [8] investigated the effect of an additional ES after an initial cholecystectomy in preventing recurrent ABP events. Their data showed a 0% rate for recurrent ABP events after cholecystectomy plus ES compared with a 19% rate for recurrent ABP events after cholecystectomy alone and 2% after ES alone. These data were not confirmed by Kahaleh et al. [79], who observed no difference between ES and ES plus cholecystectomy in preventing recurrent ABP (2.1% vs 3.0%). Furthermore, the high rates of ABP recurrence after cholecystectomy in the Hammarstrom et al. [8] study were not confirmed by Kaw et al. [7], who reported a rate of 2.4%. Boerma et al. [80] investigated the outcome of a cholecystectomy for patients whose symptomatic CBD stones, ABP, or both were treated by an ERCP and ES. The patients were randomized into two groups: group 1 (ERCP and ES plus cholecystectomy) and group 2 (ERCP and ES plus a wait-and-see policy). They observed significantly higher rates of conversion from laparoscopic to open procedure in the wait-and-see group than in the cholecystectomy group (55% vs 20%; p = 0,01). This also was observed by Allen et al. [86] in a prospectively collected database (25% vs 4%; p\0.01). However, these observations were not confirmed in the meta-analysis by McAlister et al. described earlier.

CONCLUSION

Endoscopic sphincterotomy with or without an additional cholecystectomy offers better protection than cholecystectomy alone in terms of reducing the number of recurrent ABP events. An additional cholecystectomy after ES is indicated because studies suggest an added reduction in mortality and morbidity. The proper timing of the cholecystectomy has not been studied and is based on expert opinion. The current consensus is that surgery should be used for mild cases during the same hospital admission and severe cases after 6 weeks. To prevent recurrent ABP events or other gallstone-related disease, CBD stone clearance is an important issue. Therefore, diagnosing CBD stones to establish the proper indication for ERCP with ES and stone removal is an important and clinically relevant item. For this, MRCP and EUS are instrumental. Randomized clinical trials comparing the long-term effects of cholecystectomy and ES versus cholecystectomy alone for APB are indicated.

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List of abbreviations

AIP	Autoimmune pancreatitis
AIV	Autoimmune vasculitis
ALT	Alanine transferase
ANCA	Anti-neutrophil cytoplasmic antibody
AZA	Azathioprine
CD	Crohn's disease
CP	Chronic pancreatitis
ERCP	Endoscopic retrograde cholangio and pancreaticograpy
IBD	Inflammatory bowel disease
MP	Mercaptopurine
MPO	Myeloperoxidase
NCGN	Non-classifiable glomerulonephritis
PR 3	Proteinase 3
TIAP	Thiopurine-induced acute pancreatitis
UC	Ulcerative colitis
IBDU	IBD Unclassified

CHAPTER 5

AZATHIOPRINE OR MERCAPTOPURINE INDUCED ACUTE PANCREATITIS IS NOT A DISEASE SPECIFIC PHENOMENON

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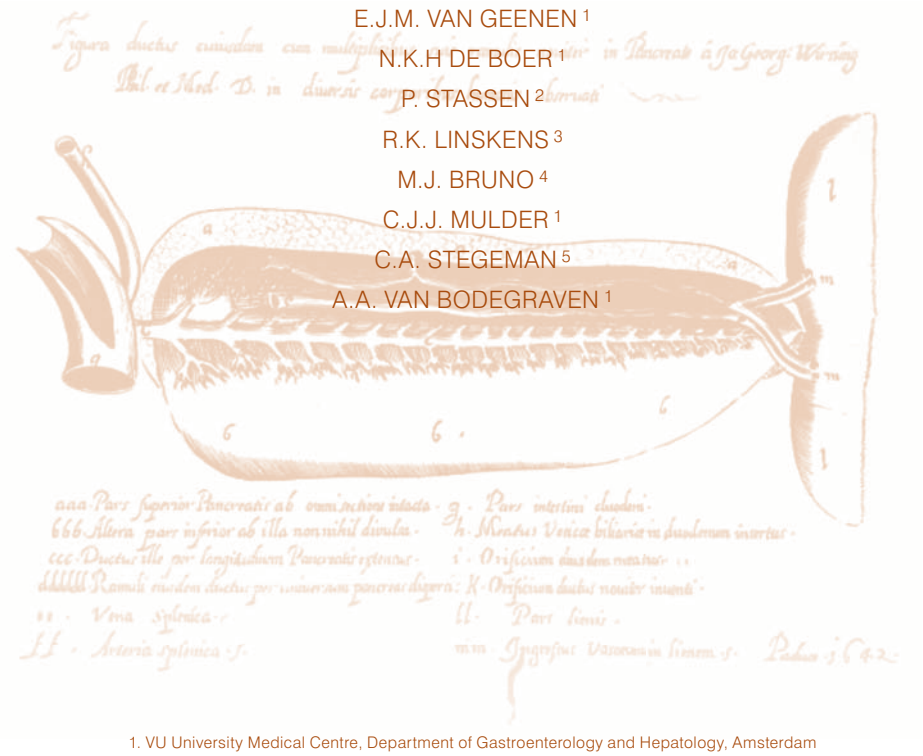

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ABSTRACT

Background. Several reports suggest an increased rate of adverse reactions to azathioprine (AZA) in patients with Crohn's disease (CD).
Aim. To compare the incidence of thiopurine-induced acute pancreatitis (TIAP) in patients with IBD with that in patients with vasculitis.
Methods. This retrospective analysis was performed using data collected in three databases by two university hospitals (241 patients with IBD and 108 patients with vasculitis) and one general district hospital (72 patients with IBD).
Results. The cumulative incidence of TIAP in CD equalled that of ulcerative colitis (UC) (2.6% vs. 3.7%), and this did not differ from vasculitis patients (2.6% vs.1.9%). Additionally, the cumulative incidence of TIAP in UC-patients was not different from vasculitis patients. In the IBD group, 100% of TIAP-patients were female , whereas in the vasculitis group the two observed TIAP cases (n=2 out of 2) concerned males (p=0.012).
Conclusions. In this study, the alleged higher cumulative incidence of TIAP in CD compared to vasculitis or UC patients was not confirmed. Female gender appears to be a risk factor for developing TIAP in IBD patients.

INTRODUCTION

Drugs are thought to be a relatively rare cause of acute pancreatitis, with an estimated incidence between 1:1000 to 1:50[1, 2]. The true incidence of drug related pancreatitis is **hampered** by underreporting of cases by clinicians to the appropriate authorities. Nevertheless, many drugs have been suspected of causing pancreatitis with evidence mainly derived from case reports and small cohort studies. Diagnosis of drug-induced pancreatitis may be cumbersome as in cases with mild to moderate severity abdominal complaints may not stand out against regular symptoms of the underlying disease. Diagnosis and subsequent identification of the culprit pathogenic drugs is pivotal since disease course may worsen if the causative drug is not withdrawn[2]. Few data exist on the mechanisms causing drug-induced pancreatitis. Clinically, certain subpopulations such as children, women, the elderly, and patients with inflammatory bowel disease appear to be at higher risk[1, 2].
The thiopurine bases 6-mercaptopurine (MP) and azathioprine (AZA) are widely used in the treatment of patients with inflammatory bowel disease (IBD) and vasculitis. These immunosuppressives, usually intended for maintenance treatment, reduce the need for corticosteroids in about 75% of patients. Median response time of effectiveness is three to four months[3-6]. Remarkably, several reports suggest an increased rate of AZA induced pancreatitis in patients with Crohn's disease (CD) compared to other patients groups also suffering from idiopathic, chronic inflammatory conditions with auto-immune characteristics[7, 8]. Thiopurine use is known to induce adverse events in a fairly high percentage ranging from 10 to 29%[9, 10]. Apparently, adverse events are not only drug-class specific, but may be disease-related as well[7, 8]. In this study we investigate whether the incidence of thiopurine induced acute pancreatitis (TIAP) is increased in patients with IBD, and CD in particular, in comparison with patients with autoimmune vasculitis.

METHODS

Patient selection and data collection

The study was performed with data enclosed in three databases from two university hospitals and one general hospital in the Netherlands. The IBD patients were treated at the VU University Medical Centre (VUMC) in Amsterdam and St-Anna-Hospital (SAH) in Geldrop. The vasculitis patients were treated at the University Medical Centre of Groningen (UMCG). In all three databases (VUMC, UMCG and SAH) information was collected regarding patient characteristics, dosage of thiopurines, side effects, co-medication, duration of thiopurine use, and reason for discontinuation of AZA/MP. In the VUMC-IBD database, patients with IBD were

studied in an interception cohort from 01-01-2000 till 01-01-2007. The database is maintained daily to monitor IBD patients and their treatment. Diagnosis of IBD was established and classified by an experienced IBD-gastroenterologist (AvB). Azathioprine or MP was started in a therapeutic step-up approach similar to guidelines that recently have been advocated in the ECCO guidelines of IBD[11-13]. Information of IBD patients from the St Anna Hospital, a general hospital in Geldrop, was extracted from an IBD-database dating back to January 2000. Diagnosis of IBD was established by two gastroenterologists (RL and his colleague). Both were trained to manage thiopurine therapy similar to that at the VUMC.

ANCA-positive-vasculitis patients who were treated at the UMCG with AZA were retrieved from the hospital records from the period January 1995 to February 2006. Patients were classified using the Chapel Hill Consensus Conference definitions[14]. All patients were initially treated with oral cyclophosphamide 1.5-2.0 mg/kg/d, in combination with corticosteroids. When remission induction was achieved for a three-month period, patients switched to AZA 1.5-2.0 mg/kg/d. A complete blood count was performed at week 2 and 4 after baseline to adjust the dose of AZA to maintain white blood cell count above 4.0 10^9/l. From twelve months onwards, the daily dose of AZA was tapered by 25 mg every three months to 1.5mg/kg bodyweight.

Of all patients, thiopurine dosage, duration of therapy, laboratory results, body mass index, smoking habits, time to develop TIAP, and co-medication were collected. TIAP was defined as serum amylase or lipase equal or more than two times the upper reference limit of normal (200IU/l), combined with compatible clinical signs, such as chronic or acute epigastric pain with or without radiation to the back. Other aetiologies of acute pancreatitis (hypertriglycaemia, excessive alcohol use: ≥5 units per day, biliary causes and hypercalcaemia) had to be excluded.

Cumulative incidence was defined as the number of new cases within a specified time period divided by the size of the population initially at risk. The time period used is the mean time that thiopurines were used by a specific cohort. The incidence rate was defined as the number of new cases per unit of person-time at risk, correcting for possible differences in mean follow-up time (thiopurine use in this study) between different studies. In this study, we defined the incidence rate as the number of new cases of acute pancreatitis or TIAP/100000/year.

Statistical analysis

To compare proportions of TIAP in different treatment groups, an independent samples t-test, chi-square test and Fischer-exact test were used with a $p < 0.05$ considered as significant (SPSS version 14, Chicago, U.S.).

RESULTS

Between 2000 and 2007, 1002 patients were collected in the VUMC database. Twenty-eight patients were excluded because they eventually proved to have no IBD, leaving 974 patients. Of these, 733 patients did not use thiopurines in the studied intercept. Consequently, 241 patients were available for analysis. Crohn's disease was diagnosed in 162 patients, ulcerative colitis (UC) in 76 patients, and colitis of undetermined origin (IBD-U) in 3 patients (table 1). In the SAH database 424 patients with IBD were collected. Seventy-two IBD patients used AZA or MP.

Table 1 Patient characteristics VUMC, SAH and UMCG

	VUMC	SAH	UMCG	IBD versus Vasculitis
Total on AZA/MP	241	72	108	
MP (N (%))	48 (20%)	5 (7%)	-	P=0.0023
AZA (N (%))	192 (80%)	67 (93%)	108 (100%)	P<0.0001**
Gender: male (%)	38.6	52.8	59.3	P<0.0001*
Average age in yrs (SD)	42.6 (13.1)	46.3 (14.3)	51.9 (14.7)	P<0.0001**
CD (N (%))	162 (67%)	34 (47%)	-	
UC (N (%))	76 (33%)	32 (44%)	-	
IBD-U (N (%))	3 (1%)	6 (8%)	-	
PSC	11 (3.5%)	0 (0%)		
Mean BMI in kg/m*m (SD)	23.8 (4.5)	24.2 (3.7)	27.0 (4.7)	P<0.0001*
Mean dose AZA mg/kg (SD)	1.87 (0.60)	1.82 (0.65)	1.43 (0.49)	P<0.0001*
Mean dose MP in mg/kg (SD)	1.15 (0.42)	0.89 (0.30)	-	
Mean age at diagnosis in years (SD)	27.0 (13.5)	35 (14.6)	51.1 (17.0)	P<0.0001*
Mean age at start thiopurines in years (SD)	34.8 (12.1)	40.25 (14.3)	51.1 (17.0)	P<0.0001*
Mean thiopurine use in months (SD)	35.8 (43.3)	27.2 (30.9)	38.8 (28.8)	P<0.0001*
ANCA+-vasculitis MPA (n) NCGN (n) WGD (n)	-	-	108 14 10 84	

* Independent samples t-test ** Chi-square test
CD=Crohn's disease;UC=Ulcerative colitis; IBD-U=Colitis of undetermined origin; BMI=Body mass index; AZA=Azathioprine; MP=Mercaptopurine; MPA=Microscopic polyangiitis; NCGN=Non-classified glomerulonefritis; WGD=Wegener's disease; PSC= primary sclerosing cholangitis

Crohn's disease was diagnosed in 34 patients, UC in 32 patients and IBD-U in 6 patients (table 1). All of the 108 ANCA-positive-vasculitis patients in the UMCG database received AZA. Fourteen patients were diagnosed with microscopic polyangiitis, 84 with Wegener's disease and ten with non-classified glomerulonephritis (table 1).

Differences between academic and general district hospital in IBD patients

A higher percentage of the IBD patients received thiopurine therapy in the academic hospital (VUMC) when compared to patients treated in the general district hospital (SAH) (24% versus 17%, P<0.001). In the academic hospital, a higher percentage of IBD patients had CD (67% versus 47%, p=0.012), a longer duration of IBD (96 versus 24 months, p=0.012) and a younger age at diagnosis (27 versus 35 years, p=0.03, see table 1). Azathioprine, next to MP use, was more commonly used in the general hospital when compared to the cohort of the university hospital (93 versus 80%, p=0.0023).

Demographic and clinical differences between IBD and vasculitis patients

Patients with IBD were significantly younger than vasculitis patients (42.6 and 46.3 years versus 51.9 years, p<0.0001). Average BMI, age at first use of a thiopurine derivative (baseline) and percentage of men were lower in the IBD group (p<0.0001). Azathioprine mean dosage was higher in the IBD group (1.87 and 1.82 mg/kg versus 1.43 mg/kg, p<0.0001, table 1). The mean duration of thiopurine use was longer in the vasculitis cohort than the IBD cohort (3.23 year versus 2.73 year, p<0.00001)

Cumulative incidence of acute pancreatitis

Overall, acute pancreatitis was diagnosed in 10 IBD patients on thiopurines. One patient was diagnosed with an alternative aetiology of acute pancreatitis, being a post-double-balloon-enteroscopy-pancreatitis. Therefore, nine patients with acute pancreatitis met the inclusion criteria for having a possible TIAP (9/313 = 2.9%) in the IBD population (VUMC plus SAH). Two patients with IBD, who were diagnosed with TIAP (normal liver functions and absence of choledocholithiasis on abdominal ultrasound), had a history of acute biliary pancreatitis for which they underwent an endoscopic retrograde cholangiopancreaticography (ERCP) with endoscopic sphincterotomy and subsequent laparoscopic cholecystectomy. In the UMCG vasculitis database (n=108), 2 patients with vasculitis developed TIAP, which resulted in a 1.9% cumulative incidence of TIAP (table 2). Both patients lacked a history of alcohol abuses, cholecystectomy or endoscopic sphincterotomy.

Table 2 Patient characteristics: the cases of TIAP

	Sex	Age (y)	IBD or AIV	BMI M^2/kg	Dose mg/kg	Duration AZA use	Smoking	Co-medication	Maximal Amylase
1	F	35	CD	24.2	1.22	30d	+	2	426
2	F	57	CD	26.8	1.2 (MP)	28d	+	1, 2	489
3	F	23	UC	26.7	1.26	6d	-	1,3	200
4	F	53	CD	22.7	0.83	25d	+	3	493
5	F	26	UC	24.5	2.0	25d	-	1,2,3	1234
6	F	32	CD	21.8	2.0	21d	+	1	1014
7	F	42	UC	21.8	1.0	5d	-	2,3	445
8	F	30	CD	19.8	2.0	27d	+	2,3	3208
9	F	18	UC	21.8	2.0	25d	-	1	290
10	M	65	NCGN, MPO+	24.9	0.63	240d	-	1	4396
11	M	60	WGD PR3+	22.5	1.37	365d	-	-	687
Average							-	-	-
IBD		35.1		25.2	1.7	<30d			
Vasculitis		62.5		23.7	1.0	> 8mnd			

* Max [Amylase] = maximal documented amylase concentration during pancreatitis attack (reference level: 0-100 U/l)
F= female; M= male; Concomitant medication: 1= prednisone, 2 = budesonide, 3 = mesalazine; IBD=Inflammatory Bowel Disease; AIV=autoimmune vasculitis; CD = Crohn's disease; UC = Ulcerative colitis;Y = years; d = days; NCGN = Non-classifiable glomerulonephritis; MPO = Myeloperoxidase; PR 3 = Proteinase 3, MP = Mercaptopurine

Table 3 Cumulative incidence of thiopurine induced acute pancreatitis (TIAP)

Diagnosis	CD	UC	IBD-U	Vasculitis	Total
Male / Female (n)	70 / 126	59 / 49	6 / 3	64 / 44	199 / 222
TIAP: M / F (n)	0 / 5	0 / 4	0 / 0	2 / 0	2/ 9
Total (n)	196	108	9	108	421
%TIAP Total	2.6%	3.7%	0%	1.9%	2.6%

M = male; F = Female; TIAP = Thiopurine induced acute pancreatitis; CD = Crohn's disease; UC = Ulcerative Colitis; IBD-U = IBD Unclassified

In the IBD group TIAP was equally often observed in CD-patients and UC-patients (2.6% and 3.7%, p=0.79). This was not statistically significantly higher in comparison with the cumulative incidence in the vasculitis group (2.9% vs. 1.9%, p = 0.735). Cumulative incidences of patients with CD, UC and vasculitis were equal (2.6% and 3.7% vs. 1.9%, p= 0.443 and p=1.00, respectively). The incidence of TIAP in IBD was higher in women than in men (5.1% vs 0%, p=0.012). No difference in TIAP cumulative incidence was observed between patients in the university hospital (VUMC) and patients from the general district hospital (SAH: p=0.79). Another difference between the IBD and vasculitis patients was the time lag between initiation of AZA/MP therapy and the development of TIAP. All IBD cases developed TIAP within 1 month, whereas in vasculitis patients this time interval was more than 8 months (see table 2, p<0.0001). The cumulative incidence of TIAP in patients on MP compared to AZA was similar, respectively: 1.9% vs 3.0% (p=0.58).

Incidence rate of acute pancreatitis

The incidence rate of acute pancreatitis (due to any cause) in this IBD-cohort was calculated by approximation: ten patients with acute pancreatitis divided by a total of 313 IBD patients divided by 2.73 years of follow up, times 100.000, resulting in an incidence rate of 1070/100.000/year. The incidence rate of TIAP in the IBD cohort (thus, related to thiopurine use) was calculated to be: nine cases in 313 patients in an average 2.73 year, resulting in 1053/100.000/year. In the vasculitis group a similar calculation was performed: two patients with acute pancreatitis divided by a total of 108 patients with vasculitis divided by 3.23 years of follow-up, times 100.000, which resulted in an incidence rate of 573/100.000/year.

Incidence rate of TIAP in patients with IBD not using thiopurines was calculated using the university database. Of the 733 patients with IBD, not using thiopurines, the follow-up of 658 patients could be retrieved, which resulted in a mean follow-up of 7.7 years. In this IBD-cohort, 4 patients with acute pancreatitis were retrieved (two patients with acute pancreatitis without identifiable cause, one mesalazine-

induced acute pancreatitis and one following double-balloon-enteroscopy), resulting in a cumulative incidence of 0.6%. The incidence rate in this group was 4/658/ 7,7 times a 100000 or 79 cases of acute pancreatitis/100.000/ year. Since these calculations represent a rough approximation of the true incidence rate, additional analytical statistical elaboration was not performed.

DISCUSSION

In this study we assessed the cumulative incidence of TIAP in 313 patients with IBD and 108 patients with vasculitis. The cumulative incidence of acute pancreatitis in all patients was 2.4%, irrespective of the causative factor. The overall cumulative incidence of TIAP was 2.1%. The cumulative incidence of TIAP was not statistically significant different between patients with CD (2.6%), UC (3.7%) or IBD (2.9%), when compared to patients with vasculitis (1.9%). Therefore, TIAP seemed not to be a disease specific phenomenon.

The cumulative incidence of TIAP in IBD patients varies in literature between 1% to 6%[7, 8, 15-18], which is in line with our findings (2.9 %). Incidence of TIAP in patients with vasculitis is not widely reported. Apart from a few case reports, only one retrospective study reported no occurrence of TIAP in vasculitis (n=85, Wegener's disease) [7]. In our series; the cumulative incidence of TIAP in patients with vasculitis was relatively low (1.9%), but in the range of TIAP in IBD patients. Intriguingly, TIAP developed in one patient with Wegener's disease (n=1/84; 1.2%).

Previous series reported an increased cumulative incidence of TIAP in CD-patients compared to UC, autoimmune hepatitis and autoimmune vasculitis-patients[7, 8]. Several theories have been put forward to explain this observation: 1) a higher percentage of smokers (Relative Risk 3.59)[19], 2) duodenal involvement of CD (5-12%)[8], and 3) a higher prevalence of choledocholithiasis or sludge[8]. In our series, however, UC and vasculitis patients who developed TIAP did not smoke, and duodenal involvement of CD was not present. Additionally, the cumulative incidence of TIAP did not differ between CD and UC patients (2.6 vs. 3.7%).

The two patients with vasculitis developed TIAP after an eight month period which is a much longer interval when compared to patients with IBD in whom TIAP occurred within 30 days ($p<0.0001$). In IBD patients an "idiosyncratic" reaction appears to be the cause of TIAP, and this 30 days interval of developing TIAP is also reported by others[8, 20]. Thiopurines are usually initiated in patients already using corticosteroids, suggesting a direct toxic component in the development of TIAP.

Corticosteroids were simultaneously used in 4 out of 9 patients of this series (prednisone). A female predominance in patients with TIAP has been described before in patient series suffering from IBD, but not as stern as in this cohort of IBD patients[7, 8]. It is unclear what this observed susceptibility to TIAP caused in female IBD patients. Both vasculitis patients who developed TIAP were man.

Regarding the aetiology of adverse effects of thiopurines several pharmacodynamic and metabolic options have been suggested in literature [21-23]. Conflicting data have been published concerning the role of the thiopurine metabolizing enzyme inosine triphosphate pyrophosphatase (ITPase) in developing TIAP[22-24] . Patients with diminished ITPase may be at an increased risk of developing TIAP. Whether TIAP is a drug class (thus thiopurine) induced phenomenon is recently challenged by reviews on the use of the non-conventional thiopurine 6-tioguanine[25] .6-Tioguanine-induced pancreatitis is rare and has been reported to occur in only 1% of IBD patients previously intolerant to the classical thiopurines AZA and/or MP. Remarkably, 10% of this 6-tioguanine-using group had developed TIAP when using AZA before [26].

An average annual incidence rate of a first attack of acute pancreatitis of approximately 12.4-15.9/100.000/year has been reported in a reference Dutch population (1988-2003)[27]. The incidence rate in these cohorts of vasculitis and IBD-patients on thiopurines is approximately 38 (573/15) and 75 (1070/15) times higher than the observed yearly incidence rate in the Netherlands. This increased relative risk (allegedly well above 10) strongly corroborates the association between thiopurine use and acute pancreatitis. A much lower incidence of acute pancreatitis of 79/100.000/year in the IBD patients not using thiopurines compared to the above mentioned cumulative incidences of acute pancreatitis in IBD patients using thiopurines corroborates an association between thiopurines and acute pancreatitis.

On a statistical level the cumulative incidences did not differ between patient groups, but the absolute incidence rates for IBD 1053/100.000/year was twice that of the vasculitis group, which was within the range of the results reported by Weersma et al and Baja et al, both reporting an increased incidence rate of TIAP in CD if compared to other autoimmune diseases[7, 8]. In the study of Baja, the definition of TIAP was restricted to a one-month follow-up, which potentially excluded late onset TIAP[8]. Therefore, the results of our study should be compared prudently with this study, as TIAP in (our) non-IBD patients developed in general much later. However, implying their inclusion criteria and definitions, the TIAP percentage would be 0% in the vasculitis group in our series, which nearly equals their findings. The study by Weersma and colleagues only calculated the incidence rate, which is

not corrected by the follow-up time[7]. Consequently, a comparison with our findings would probably be biased by this difference in duration of follow-up.

The incidence of acute pancreatitis is increased in IBD patients, compared with the general population[28]. An acute pancreatitis incidence of respectively 1,4% and 1,6% has been reported in cohorts of 852 and 5073 IBD-patients, respectively [29, 30]. This is in line with our observations in non-thiopurine-using IBD patients (79/100.000/year) plus thiopurine-using IBD-patients (1070/100.000/year) resulting in a total of 1.1% acute pancreatitis per year in this IBD cohort.
In addition, chronic pancreatitis (CP) is associated with IBD with an estimated 250 times higher incidence in patients with IBD (1.2%) compared to the average risk in the general population[31]. Finally, a recent report by Ravi and colleagues documented a substantial, relatively increased, proportion of IBD patients in a cohort of patients suffering from autoimmune pancreatitis (AIP) [32].

Primary sclerosing cholangitis (PSC) ,which is more prevalent in patients with IBD (2-10%)[33], is associated with an increased incidence of acute pancreatitis[34, 35]. PSC in patients on thiopurines was diagnosed in 11 patients of the university database (4.6%%). No cases of PSC were reported in the district hospital (0%). Resulting in a overall PSC incidence of 3.5% in IBD patients, which is in line with the reported findings. However, none of the patients with acute pancreatitis in our databases were diagnosed with PSC.

In this study, neither ALT increase was observed nor alcoholic abuse was reported in relation with the attacks of acute pancreatitis. Clinical features of chronic pancreatitis were not present in our TIAP cases. Since thiopurine use is a well-known risk factor for acute pancreatitis, it cannot be excluded that clinicians refrained from a full scaled diagnostic run, including MRI or CT-scan, assessment of all known metabolic risk factors and exclusion of rare pathogenetic causes of pancreatitis. This potential flaw probably applies more to IBD-patients as TIAP is uncommon in vasculitis patients, and therefore more extensively investigated by treating physicians. Rechallenge with thiopurines to corroborate or ascertain the diagnosis TIAP is unusual in clinical practice due to the high risk of inducing a potentially severe and life threatening disease such as TIAP is.

The duration of thiopurine use in the vasculitis patient cohort was longer than in the IBD cohort (3.23 years versus 2.72 years, $p<0.0001$). However, since TIAP in IBD-patients developed within 30 days of thiopurine use, a longer follow-up time was not likely to increase the number of TIAP cases.

Differentiation between vasculitis induced acute pancreatitis and drug induced pancreatitis is difficult, because vasculitis may induce pancreatitis itself[36]. The diagnostic accuracy of TIAP in these autoimmune vasculitis patients may therefore be hampered, in particular since our patients had no re-challenge with AZA, and, hence, vasculitis-induced pancreatitis, although an uncommon finding, cannot be ruled out. Consequently, the true cumulative incidence of TIAP in autoimmune vasculitis patients might be (slightly) lower.

In conclusion, contrary to existing literature data, we observed a statistically comparable cumulative incidence of TIAP in patients with IBD and vasculitis. In IBD patients, a female gender is associated with the risk for developing TIAP. In vasculitis patients, TIAP tends to develop later than in IBD-patients, which may point towards a different aetiology.

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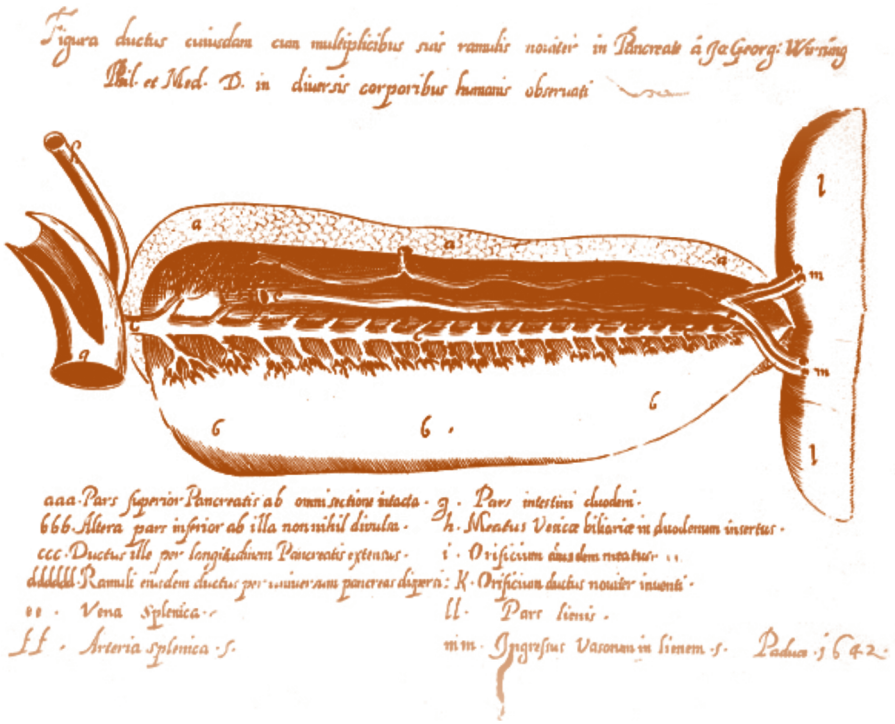
5

PART 2

CLINICOMORFOLOGICAL STUDIES ON PANCREATIC LIPOMATOSIS AND PANCREATIC INFLAMMATION

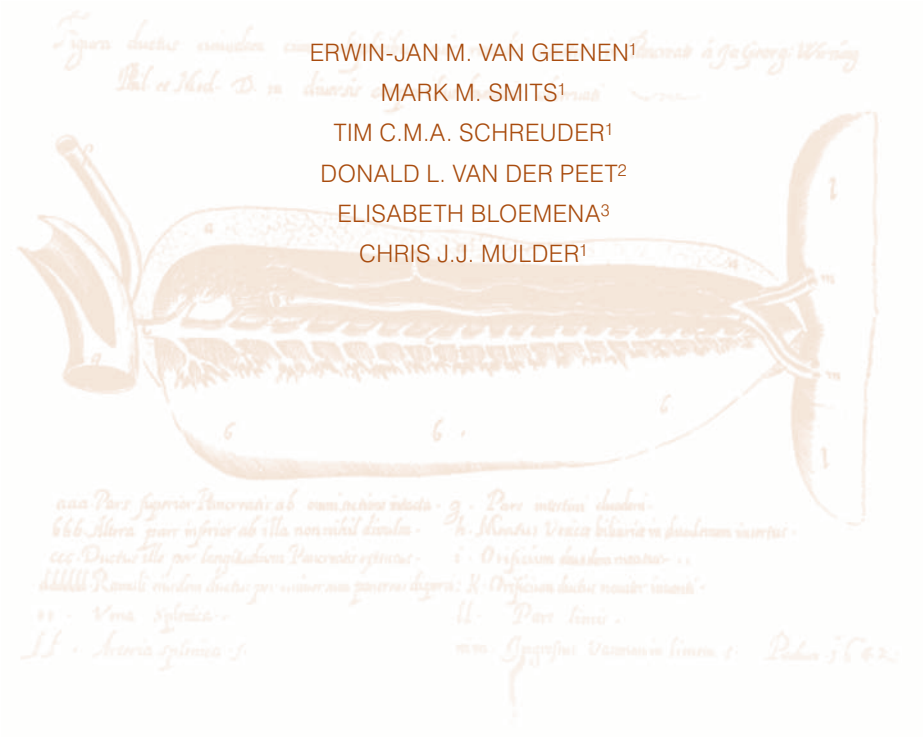


List of abbreviations

BMI	body mass index
PL	pancreatic lipomatosis
PS	pancreatic steatosis
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NAFPD	nonalcoholic fatty pancreas disease
NAS	NAFLD activity score
T2DM	type 2 diabetes mellitus

CHAPTER 6

NONALCOHOLIC FATTY LIVER DISEASE IS RELATED TO NONALCOHOLIC FATTY PANCREAS DISEASE



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ABSTRACT

Objectives: Obesity and insulin resistance cause fatty infiltration of many organs, including the pancreas (pancreatic steatosis [PS]) and the liver (nonalcoholic fatty liver disease [NAFLD]). In contrast to NAFLD, patho-physiological mechanisms and clinical relevance of PS remain unknown. This study aimed to identify a possible relation between PS and NAFLD.

Methods: In this study including postmortem collected material of 80 patients, clinical and histological data were collected and revised. Patients with hepatic or pancreatic disease and alcohol abuse were excluded. Nonalcoholic fatty liver disease activity score was used for grading the histology of the liver, whereas pancreatic lipomatosis score assessed PS. Ordinal logistic regression was used to analyze correlations.

Results: Interlobular and total pancreatic fat were both related to NAFLD activity score in patients without steatogenic medication ($P = 0.02$ and $P = 0.03$, respectively). When corrected for body mass index, no relation could be found. Total pancreatic fat was a significant predictor for the presence of NAFLD ($P = 0.02$). Presence of intralobular pancreatic fat was related to nonalcoholic steatohepatitis; however, total fat was not.

Conclusions: This study demonstrates that NAFLD and PS are related. This relationship seems to be mediated by general obesity. Intralobular pancreatic fat is associated with nonalcoholic steatohepatitis.

INTRODUCTION

Obesity is becoming an endemic problem with tremendous prevalence numbers (1). In the period of 1981 till 2006, the prevalence of obesity among adults in the Netherlands increased from 5.1% to 11.3% (2). Obesity is related to a variety of diseases, such as cancer, metabolic syndrome, and cardiovascular disease (1,3,4). In humans, obesity and associated insulin resistance can cause fat infiltration of striated muscle, the heart, the liver, and the pancreas (5). Excessive storage of fat in pancreatic tissue has been termed pancreatic lipomatosis (PL), first described by Ogilvie (6). The term lipomatosis is old and is now replaced by steatosis. Literature regarding pancreatic steatosis (PS) is scarce, and its pathophysiological mechanisms and clinical relevance are largely unknown. The degree of PS is correlated with age and BMI (7,8). Moreover, Stamm (8) demonstrated a significant association of severe generalized atherosclerosis, adult-onset diabetes, and pancreatic fibrosis with PS. Recently, Tushuizen et al. (9) observed increased pancreatic lipid content, measured by ^{1}H magnetic resonance (MR) spectroscopy, in a prospective study of 36 patients with A-cell dysfunction, a finding that was not confirmed by Saisho et al. (10) who performed a computed-tomography based retrospective study on 1886 adult patients. Furthermore, PS is associated with several benign and malignant diseases, such as cystic fibrosis, chronic pancreatitis, steroid therapy, Shwachman-Diamond syndrome, pancreatic pseudohypertrophia, Johanson-Blizzard syndrome, viral infection, and pancreatic duct obstruction (11-14). Pancreatic steatosis also increases the risk of postoperative fistulas in pancreatic surgery and promotes dissemination and lethality of pancreatic cancer (15,16).

In the liver, accumulation of triglycerides in the absence of excess of alcohol use and other chronic liver diseases has been defined as nonalcoholic fatty liver disease (NAFLD). After exclusion of secondary causes (eg, steatogenic medication), a strong association exists between NAFLD, insulin resistance, and the metabolic syndrome (17,18). As a consequence of the increasing prevalence of obesity, NAFLD is becoming the most common cause of chronic liver disease.19 It ranges from simple hepatic steatosis through nonalcoholic steatohepatitis (NASH) to liver cirrhosis and increased risk for developing hepatocellular carcinoma (20). Simple hepatic steatosis is of minor clinical importance because less than 5% develops end-stage liver disease (21). However, in patients with NASH, characterized by lobular inflammation and ballooning degeneration of hepatocytes, approximately 20% develops cirrhosis, liver failure, and/or hepatocellular carcinoma (21). Some authors introduced the entity nonalcoholic fatty pancreas disease (NAFPD) for PS, thereby suggesting a possible relation between NAFLD and NAFPD/PS (22,23).

However, an association of NAFLD and PS has never been demonstrated in larger cohort studies. The objective of this study was to analyze this relation between PS/NAFPD and NAFLD.

MATERIALS AND METHODS

In this retrospective study, autopsy material of the pancreas and the liver of deceased patients admitted to the VU University Medical Centre, Amsterdam, the Netherlands, was collected and reviewed. Patients of 18 years and older were included (24). Exclusion criteria were (1) features consistent with hepatic or pancreatic disease collected from medical files, (2) major abdominal surgery in patient's medical history: major gastrointestinal surgery (small intestinal surgery, Billroth surgical intervention, Roux-en-Y anastomosis, hepatobiliary, and pancreatic surgery due to possible aspecific lymphocytic infiltration of liver tissue), (3) documented history of excessive alcohol intake (≥21 drinks per week for men and ≥14 drinks per week for women), and (4) severe postmortem changes that hampered histological features. The aim of this study was to evaluate the relation between obesity-related NAFLD and PS; therefore, (5) patients who used steatogenic medication (eg, methotrexate, highly active antiretroviral therapy, amiodarone, and glucocorticoids (25) or with unknown previous use of medication were excluded.

Histopathological Study

Autopsy material was assessed by an experienced hepatobiliary histopathologist (EB) and 2 research fellows (MS and EG), all blinded for patients' clinical and laboratory data. Only 1 liver slide and 1 pancreas slide were available per patient. Unfortunately, it was not known where in the liver and the pancreas these samples were taken. Different scoring systems were used for the liver and the pancreas.

Liver

Hepatic steatosis and inflammation were graded according to the NAFLD activity score (NAS) (24). Slides were stained with hematoxylin and eosin sand assessed regarding the presence of macrovesicular steatosis (0-3), lobular inflammation (0-2), hepatocellular ballooning (0-2), and fibrosis (0-4). The sum of individual grades, excluding fibrosis, represents NAS. In addition, the overall amount of hepatic steatosis (macrovesicular and microvesicular) was scored (0-3).

Pancreas

Because there is no evidence-based scoring system for PS, our research group developed a new grading system: the PL score (article under submission). This

grading system emphasizes the distribution of intralobular, interlobular, and total pancreatic fats. In our validation process, we have found a high interrate variability (kappa 0.89) and a low intrarater variability (kappa, 0.10). Therefore, all pancreatic slides were scored by 1 panel (MS, EG, and EB). With this system, the quantity of adipocytes per microscopic pancreas compartment (interlobular and intralobular) was graded according to 5 separate groups: 0, 0% to 7% adipocytes; 1, 8% to 14%; 2, 15% to 25%; 3, 26% to 50%; and 4, greater than 51%. When grading total amount of fatty infiltration (interlobular and intralobular), an additional group was added: 5, greater than 75%. In addition, the presence of lymphocytes was noted.

Clinical Data

From (electronic) medical files and autopsy reports, clinical and biochemical data were collected in a central database. Collected clinical data consisted of sex, BMI, age, blood pressure, history of alcohol and tobacco abuse, and medical history, in particular cardiovascular, liver, and gastroenterological diseases, diabetes mellitus, and cause of death. Body mass index was calculated from the data noted in autopsy reports. Biochemical data, such as viral serologic data (eg, hepatitis B and C antibodies), autoimmune serologic data (antinuclear factor, smooth muscle antibodies, and mitochondrial antibodies), and storage diseases (iron and copper studies), were collected. The use of steatogenic medication and medication used in patients with the metabolic syndrome (eg, antihypertensive, antidiabetic, and lipid-lowering medication) within the last 12 months were noted.

Statistical Analysis

Univariate ordinal logistic regression was used to test the relation between ordinal histological parameters. Binary parameters were analyzed by binary logistic regression. Multivariate analysis (forward stepwise ordinal regression) was performed to correct for BMI and sex. A $P \leq 0.05$ was considered to be statistically significant. Results are presented as ordinal regression coefficients (B) and P values. All analyses were performed using SPSS software version 15 for Windows (SPSS, Chicago, Ill).

Patient Characteristics

In total, more than 900 autopsies were performed in the VU University Medical Center from January 2005 till December 2007. In this period, 598 autopsies were performed on clinical patients of the VU University Medical Center. Of these patients, 415 met the inclusion criteria and were enrolled in this study. Eventually, 335 subjects were excluded predominantly because of inferior quality of the histological material due to postmortem changes or absence of histological material. Six patients were excluded because of major abdominal surgery: 2

Whipple operations, 1 Roux-en-Y anastomosis, 1 Billroth II anastomosis, 1 hepatitis e causa ignota after small intestinal surgery, and 1 right extended hemihepatectomy. Thirty-four patients were excluded because they used steatogenic medication. Thirty-six patients had an unknown medication history and were therefore excluded. Characteristics of 80 eligible patients are summarized in Table 1. There were no patients with cryptogenic cirrhosis.

Table 1 Patients' characteristics (mean ± sd or number of cases (%))

	Patients (n = 80)
Male sex	42 (53%)
Age of death	68 ± 14
BMI (kg/m^2)	26 ± 5
NAFLD (including NASH)	37 (46%)
NASH	3 (4%)
Cause of death:	
Cardiovascular	49 (61%)
Gastro-enterologic	2 (3%)
Malignancy	14 (17%)
Other	15 (19%)

Abbreviations: BMI = body mass index, NAFLD = non-alcoholic fatty liver disease, NASH = non-alcoholic steatohepatitis

RESULTS

In Table 2, the scores for liver and pancreatic fats are given for all patients. Almost half of the patients had steatosis of the liver. Nonalcoholic steatohepatitis was observed in the minority of patients with steatosis, although the density of lobular infiltrates was generally low. Fibrosis was uncommon and, if present, of minor degree. Pancreatic lipomatosis was found in most patients. This consisted mainly of interlobular fat accumulation. Pancreatic fibrosis was uncommon. No pancreatic inflammatory infiltrates were identified.

Pancreatic and Hepatic Relations

Several statistically significant correlations between histopathologically determined pancreatic and hepatic fats could be found (Table 3). Significant relations were found between pancreatic interlobular and hepatic macrovesicular fats (B, 0.377;

Table 2 Histopathologic analysis [amount (percent %)]

			Patients
Liver	*Macrovesicular steatosis*	*0*	*46 (58)*
		1	*21 (26)*
		2	*9 (11)*
		3	*4 (5)*
	Lobular inflammation	*0*	*62 (78)*
		1	*16 (20)*
		2	*2 (2)*
		3	*0 (0)*
	Hepatocellular ballooning	*0*	*77 (96)*
		1	*3 (4)*
		2	*0 (0)*
	Fibrosis	*0*	*74 (93)*
		1A	*0 (0)*
		1B	*0 (0)*
		1C	*5 (6)*
		2	*1 (1)*
		3	*0 (0)*
		4	*0 (0)*
Pancreas	*Intralobular steatosis*	*0*	*20 (25)*
		1	*33 (41)*
		2	*12 (15)*
		3	*11 (14)*
		4	*4 (5)*
	Interlobular steatosis	*0*	*12 (15)*
		1	*26 (33)*
		2	*14 (17)*
		3	*15 (19)*
		4	*13 (16)*
	Intralobular fibrosis	*0*	*59 (74)*
		1	*14 (17)*
		2	*7 (9)*
	Interlobular fibrosis	*0*	*65 (81)*
		1	*12 (15)*
		2	*3 (4)*

P = 0.03) and NAS (B, 0.377; P = 0.03) and between total pancreatic and hepatic macrovesicular fats (B, 0.340; P = 0.04) and NAS (B, 0.348; P = 0.03).

Table 3 Relations between liver and pancreas histology [ordinal regression coefficients (p-values)]

Pancreas	Liver				
	Total fat	Macro-vesicular fat	lobular infiltration	Ballooning	NAS
Intralobular fat	*0.149 (0.425)*	*0.209 (0.276)*	*0.095 (0.682)*	*0.493 (0.297)*	*0.219 (0.250)*
Interlobular fat	*0.318 (0.053)*	*0.377* ***(0.026)***	*0.191 (0.341)*	*0.466 (0.317)*	*0.377* ***(0.025)***
Total fat	*0.298 (0.056)*	*0.340* ***(0.035)***	*0.213 (0.270)*	*0.639 (0.188)*	*0.347* ***(0.031)***

However, pancreatic intralobular fat was not related to hepatic steatosis (Fig. 1). Histological features of NASH (eg, hepatocyte ballooning and lobular inflammation) were not related to PS.

Multivariate Analysis

Body mass index was significantly related to hepatic macrovesicular fat (B, 0.172; P = 0.001), total fat (B, 0.134; P = 0.008), and NAS (B, 0.18; P = 0.001; Fig. 2). It was not related to lobular infiltration (B, 0.054; P = 0.35) or hepatocellular ballooning (B, 0.025; P = 0.84). The relation of BMI and pancreatic fat was present for intralobular fat (B, 0.119; P = 0.01), interlobular fat (B, 0.152; P = 0.002), and total fat (B, 0.155; P = 0.001; Fig. 2). No significant relation between pancreatic and hepatic fats could be demonstrated when a correction for BMI was performed performed by multivariate analysis. This phenomenon was shown to be present disregarding the distribution of pancreatic fat (Table 4). (data not shown). When corrected for age, sex, and BMI, no significant relation between hepatic and pancreatic fats could be found (Table 4).

Correction for age or sex did not statistically affect the relation of pancreatic and hepatic fats. Remarkably, male subjects failed to show a significant relation on all variables, whereas female subjects inclined to statistical significance on most variables. Correction for BMI did not change this distinction.

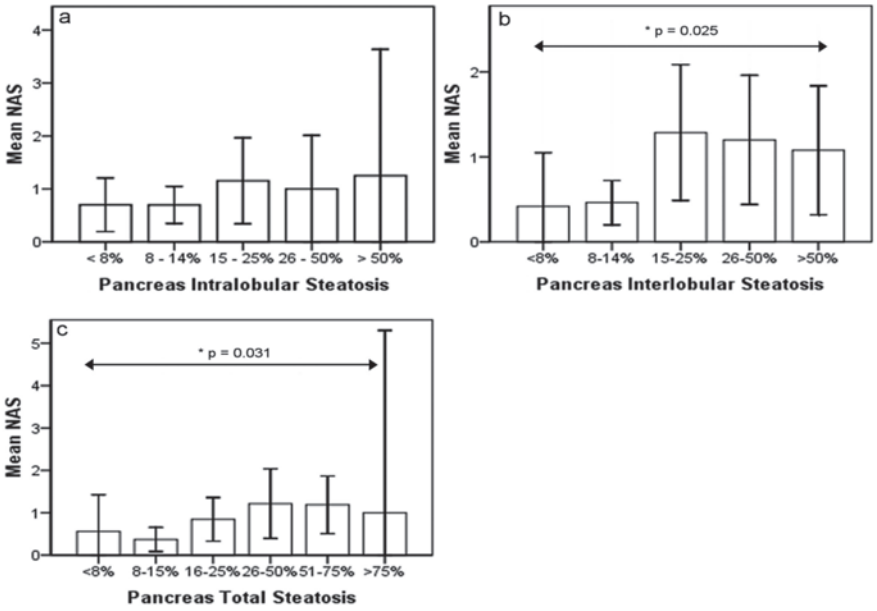

Figure 1 Relation of PS and hepatic NAS with SEM

The relation of PS (A, intralobular; B, interlobular; C, total) with hepatic NAS. Intralobular PS is not related to hepatic NAS; interlobular and total PS do. P value is calculated by ordinal logistic regression. NAS, NAFLD activity score.

Cut off Points

When dividing PS into percentiles, a cutoff point of 15% of total pancreatic fat was statistically significantly related to hepatic macrovesicular fat (B, 1.027; P = 0.04), total fat (B, 1.161; P = 0.02), and NAS (B, 1.056; P = 0.03; Fig. 3). Furthermore, a similar cutoff point of 15% of total pancreatic fat was related to the diagnosis NAFLD (B, 1.148; P = 0.02). In patients with NASH, a cutoff of 25% of intralobular pancreatic fat was significantly associated with this diagnosis (B, 2.708; P = 0.04). However, total pancreatic fat was not related to NASH.

Table 4 Relation between NAFLD en PL after correction for BMI, age and gender

Relation between Pancreatic and Hepatic		Normal	Corrected for			
			BMI	Gender	Age	BMI, Gender, Age
Intralobular fat	*Macrovesicular fat*	0.276	0.840	0.207	0.253	0.716
	Total fat	0.425	0.985	0.324	0.451	0.985
	NAS	0.250	0.942	0.154	0.248	0.763
Interlobular fat	*Macrovesicular fat*	0.026	0.485	0.039	0.017	0.582
	Total fat	0.053	0.469	0.081	0.050	0.724
	NAS	0.025	0.459	0.040	0.019	0.596
Total fat	*Macrovesicular fat*	0.035	0.710	0.046	0.022	0.784
	Total fat	0.056	0.626	0.079	0.051	0.879
	NAS	0.031	0.602	0.041	0.024	0.697

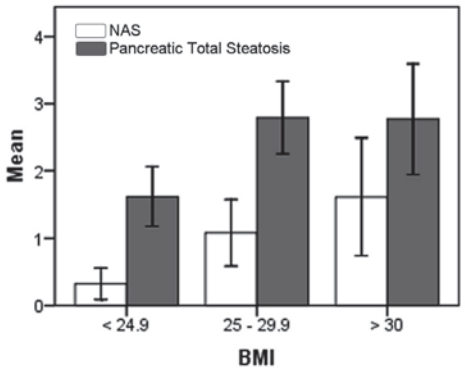

Figure 2 Relation between BMI and PS/NAFLD

The relation of BMI with NAS and total PS. Both relations are statistically significant (P = 0.001 and P = 0.001, respectively).

DISCUSSION

This is the first histopathological study focusing on the relation of NAFLD and PS. In imaging studies, Tushuizen et al. (9) using MR spectroscopy and Schwenzer et al.(26) using MR imaging could not demonstrate a relation between pancreatic and hepatic fats. Unfortunately, both studies lacked power owing to low numbers of included patients (N = 36 and N = 17, respectively). In our study, pancreatic and hepatic tissues of 80 deceased patients were reassessed and graded according to the generally accepted NAS and a newly developed PL score to find relations between NAFLD and PS.

Relations of Pancreatic and Hepatic Fats

From our analyses using the criterion standard (ie, histologic examination), a relation between various types of hepatic and pancreatic fats could be clearly demonstrated. Especially, a cutoff of more than 15% total pancreatic fat seemed to be significantly correlated with NAFLD. In particular, pancreatic fat was more significantly related to macrovesicular hepatic fat than to total hepatic fat. This suggests different pathophysiological mechanisms of macrovesicular and microvesicular fats, consistent with available data from other publications (27). Nonalcoholic fatty liver disease was stated to be associated with macrovesicular fat caused by accumulation of triglycerides, whereas microvesicular steatosis is caused by mitochondrial dysfunction due to, for instance, toxins.

Body Mass Index, Insulin Resistance, and Sex

Significant relations between PS and NAFLD disappeared when BMI correction in the multivariate analysis was performed. Therefore, this study provides evidence that BMI is involved in the pathogenesis of pancreatic and hepatic fats. Possibly, insulin resistance is involved because a strong relation between obesity and nsulin resistance has been shown (28). Insulin resistance influences peripheral lipolysis, thereby increasing the portal flux of fatty acids, which is suggested to be the “first hit” in NAFLD (29). In addition, in an overfed status, adipocytes produce inadequate amounts of adipocytokines (eg, leptin, adiponectin, and tumor necrosis factor α), causing further peripheral and hepatic insulin resistance, resulting in increased hepatic fatty acid accumulation accumulation (30-33). Whether mechanism(s) associated with fatty acids hepatic influx are similar in PS is questionable. Interestingly, in contrast to NAFLD, PS was not related to features of the metabolic syndrome (P = 0.38), which can be explained by the studies’ retrospective fashion and its accompanied missing clinical data. Another controversial argument is the presence of adipocytes in pancreatic parenchyma in comparison with lipid droplets in liver tissue.

Differences in sex regarding visceral fat and serum triglycerides have been demonstrated by many studies. In female patients, this correlation is more significant than in male patients (34). Nielsen et al.(35) hypothesized that the export of free fatty acids (FFAs) derived from visceral lipolysis to the liver is more pronounced in female patients. Another study demonstrated only in female patients the significant correlation of insulin resistance and visceral fat (36). These findings are in accordance with this study, where a sex correction in a multivariate analysis only showed a significant correlation between PS and NAFLD in female subjects.

Pancreatic Cellular Lipotoxicity and Overt T2DM

This study demonstrates a trend of overt T2DM and quantity of total PS ($P = 0.092$). These findings confirm results of recent reports demonstrating the deleterious effects of the accumulation of FFAs on A-cell function and the development of T2DM. In murine models (Zucker diabetic fatty rats), male animals who were fed a standard diet represented significantly more hyperglycemia and FFA when compared with their female counterparts (37-39). Administration of peroxisome proliferator-activated receptor-F agonists in mice on a high-fat diet decreased pancreatic islet cell triglyceride content and consequently improved insulin secretion (40). Proposed mechanisms by which FFA causes damage to A-cell dysfunction are effects on insulin biosynthesis, preproinsulin gene expression, and expression of uncoupling proteins (5,41). Whether these data can be translated to humans needs to be clarified.

Hypothesis

We hypothesize that BMI and associated insulin resistance play an important role in pancreatic adipocyte infiltration, causing PS. In addition, insulin resistance (due to a high BMI) causes peripheral lipolysis, thereby increasing the flux of fatty acids to the liver (29). Lipolysis in the pancreatic adipocytes further increases the portal flux of fatty acids. As a consequence, hepatic insulin resistance and NAFLD develop. This implies that PS precedes NAFLD. Because this is not a prospective study, conclusions regarding the chronological order of appearance cannot be drawn.

Limitations

Some limitations of this study need to be noted. Owing to its retrospective fashion, some important data are missing, undermining the statistical power. In addition, fibrosis in histological liver samples could not be accurately assessed because no Gieson staining was performed. Numbers of patients with NASH were low and statistical analysis to demonstrate possible relations between NASH and PS therefore impaired. Another limitation is the presence of 1 histological slide per

patient and the concomitant potential for sampling error because pancreatic and hepatic fats can be irregularly distributed (34,42). Further research for unraveling PS's pathophysiological mechanism and clinical consequences on the long-term is warranted.

Conclusions

Pancreatic steatosis is a relatively new clinical entity that remains to be clarified yet. Fatty liver and fatty pancreas are related especially in women, but the relationship seems to be mediated by general obesity. Therefore, using the name NAFPD can be justified owing to the coexistence with NAFLD. Whether NAFLD and PS are caused by similar mechanisms needs to be further investigated.

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CHAPTER 7

THE CLINICAL SIGNIFICANCE OF PANCREATIC STEATOSIS

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ABSTRACT

More research is now focused on pancreatic steatosis. Multiple definitions, clinical associations and synonyms for pancreatic steatosis are described in the literature and can be confusing. The integration and comparison of several studies concerning this topic is therefore challenging. In the past, pancreatic steatosis was considered an innocuous condition, a bystander of many underlying diseases (such as congenital syndromes, hemochromatosis and viral infection). However, evidence that pancreatic steatosis (strongly associated with obesity and the metabolic syndrome) has a role in type 2 diabetes mellitus, pancreatic exocrine dysfunction, acute pancreatitis, pancreatic cancer and the formation of pancreatic fistula after pancreatic surgery is emerging. This Review focuses on the different etiological factors and the clinical consequences of pancreatic steatosis.

INTRODUCTION

The incidence of overweight and obesity is increasing each decade. the current prevalence of obesity in the USA is 33.8% and in western Europe is approximately 20% (1,2). Obesity (BMI >30) is associated with several serious diseases –metabolic syndrome, cardio vascular disease and cancer– which makes obesity a major public health issue (3–5) moreover, obesity causes fatty infiltration of organs, such as the liver (non alcoholic fatty liver disease [NAFLD] or nonalcoholic steato hepatitis [NASH]), striated muscle, heart and pancreas (6,7). The latter condition, pancreatic steatosis, was first described in 1933 by Ogilvie (8). In his human post mortem study he observed 9% pancreatic fat in lean individuals versus 17% pancreatic fat in obese individuals. Olsen *et al.(*9) reported that the amount of pancreatic fat increases significantly with age (P <0.05) and Stamm(10) found significantly more type 2 diabetes mellitus and severe generalized atherosclerosis in patients with >25% fat in their pancreas (P <0.01) (9,10). The introduction of imaging techniques such as ultra-sonography, CT and MRI, confirmed the associations of pancreatic steatosis with obesity and type 2 diabetes mellitus (11–15). However, obesity is not a pre requisite for pancreatic steatosis, as the disease also occurs in non-obese individuals (that is, patients with cystic fibrosis, iron overload, viral infections, chemo therapy and chronic alcohol abuse) (16–22). Currently, research on pancreatic steatosis focuses on several different topics, such as its association with type 2 diabetes mellitus, acute pancreatitis, pancreatic cancer and the formation of pancreatic fistula.

To date, the 'true' incidence of pancreatic steatosis is unknown owing to a lack of clear definitions and research. this review summarizes available literature on the topic of pancreatic steatosis and reports the current knowledgeof this condition. Potential clinical consequences and future research directions are also described.

REVIEW CRITERIA

A PubMed search was performed using the following search terms: "pancreatic steatosis", "pancreatic lipomatosis", "NAFPD", "fatty pancreas", "pancreatic fat", "pancreatic fatty replacement" and "pancreatic fatty infiltration". The search was limited to English, Dutch or German articles; human as well as animal studies were accepted. This search retrieved a total of 159 articles and the abstracts were carefully scanned for their clinical relevance; 84 papers were excluded from this Review (in 53 papers pancreatic steatosis was not the main topic of discussion, 26 papers did not discuss the consequences of pancreatic steatosis and five abstracts with corresponding articles could not be retrieved). Additionally, articles were selected according to our own expertise on the topic.

NOMENCLATURE

Several synonyms of 'pancreatic fat accumulation' are reported in the literature, including: pancreatic lipomatosis, pancreatic steatosis, fatty replacement, fatty infiltration, fatty pancreas, lipomatous pseudohypertrophy and nonalcoholic fatty pancreas disease (naFPD) (9,21,23–27). Unfortunately, researchers use the above-mentioned terms with several different clinical and histological identities and the integration and comparison of several studies concerning this topic is therefore challenging. After reviewing the literature on pancreatic steatosis, we formed the following concept (detailed below) on the condition and will use the nomenclature for pancreatic steatosis as outlined in table 1 throughout this review. In our opinion, pancreatic steatosis, pancreatic lipoma tosis and fatty pancreas are general terms that can be used for all forms of pancreatic fat accumulation. Steatosis is a general term for parenchymal intra cellular fat accumulation (28) and pancreatic steatosis would therefore describe accumulation of fat in islet cells or acinar cells (29). However, in the literature this term is also used for fat accumulation in adipocytes (30). We therefore believe pancreatic steatosis can be used for the description of all kinds of pancreatic fat accumulation. In our opinion, 'fatty replacement' must be reserved for cases in which damage to pancreatic acinar cells has led to their death (such as viral infection or pancreatic duct ligation), which then results in their replacement in the pancreas by adipocytes (31). Fatty replacement has been stated as being irreversible (26), whereas fatty infiltration (pancreatic infiltration of adipocytes caused by obesity (32) is possibly reversed by weight reduction and appropriate medications, such as troglitazone (33,34). Fatty infiltration, a relatively old term, will probably be replaced by the term NAFPD (25). However, we propose that the term NAFPD should be reserved for pancreatic steatosis in association with obesity and metabolic syndrome as this disease subtype is crucially different from pancreatic steatosis associated with congenital syndromes. Pancreatic lipomatosis is used as a synonym for fatty replacement of the exocrine tissue and fatty infiltration; therefore, we believe pancreatic lipomatosis can be used as a general term concerning pancreatic steatosis (26,35) whether pancreatic lipomatosis must be distinguished from lipomatous pseudo hypertrophy is unclear. Some investigators employ the latter term for the condition when the pancreas is enlarged (uniformly or focally), the exocrine system is replaced by fat, and when no association can be found with obesity (23,36) However, pancreatic steatosis also enlarges the pancreas, which can be uniform or focal, and is not always related to obesity (14,37). We therefore believe that lipomatous pseudohypertrophy is an extreme variant of pancreatic fat accumulation and is therefore not a different clinical subtype in its own right.

Table 1 Common nomenclature and proposed definitions for pancreatic steatosis

Nomenclature	Definition in literature	Proposed definition
Pancreatic lipomatosis	Fatty replacement of exocrine tissue;(26) fatty infiltration (35)	General term for pancreatic fat accumulation
Pancreatic steatosis*	Fat accumulation in islet or acinar cells;(29) fat accumulation inpancreatic adipocytes (30)	General term for pancreatic fat accumulation
Fatty pancreas	General term for pancreatic fat accumulation	General term for pancreatic fat accumulation
Lipomatous pseudohypertrophy	Enlarged pancreas; exocrine systemisreplacedwithadipocytes; not associated with obesity (23)	Extreme variant of pancreatic fat accumulation
Fatty replacement*	Death of acinar cells with subsequent replacement with Adipocytes (31)	Death of acinar cells with subsequent replacement with adipocytes
Fatty infiltration	Infiltration of adipocytes owing to obesity (32)	Infiltration of adipocytes owing to obesity
Nonalcoholic fatty pancreas disease*	Increased fat in the pancreas (25)	Pancreatic fat accumulation in association with obesityand metabolic syndrome
Nonalcoholic fatty steatopancreatitis*	Pancreatitis owing to pancreatic fat Accumulation (25,110)	Pancreatitis owing to pancreatic fat accumulation

*Suggested terms that should be made standard definitions.

DIAGNOSIS

Small amounts of pancreatic fat accumulation are common and are not associated with clinical signs and symptoms (31). By contrast, a substantially increased amount of pancreatic steatosis may be related to different clinical syndromes (type 2 diabetes mellitus, exocrine insufficiency, pancreatic cancer). Pancreatic steatosis is usually detected by abdominal imaging techniques and incidentally reported by the radiologist during clinical workup for several disorders, or during autopsy. Histology in histological examinations, an increased number of pancreatic adipocytes will be found in pancreatic tissue (Figure 1) (32).

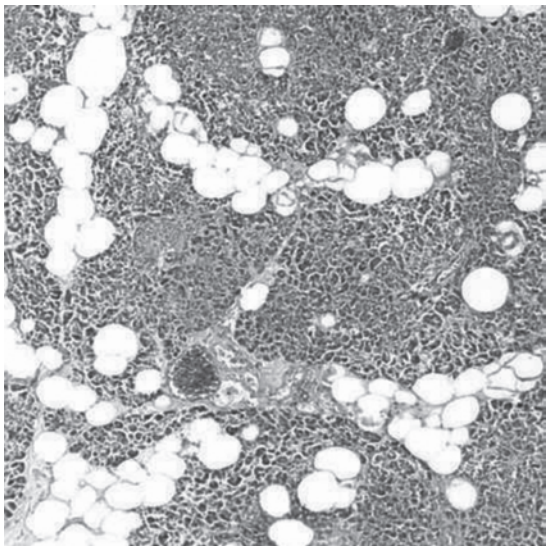

Figure 1 Histological findings of pancreatic steatosis

On microscopy, a surplus of adipocytes can be found within the pancreas (arrow). Hemotoxylin and eosin stain. Original magnification ×50.

The amount of steatosis can be quantified using a subjective scoring system (25,31,38), as no scoring system for pancreatic steatosis has been validated in patients yet, our study group has developed and validated the Pancreatic lipomatosis score (M.M. Smits and E.J.M. van Geenen, unpublished work). A more objective method for measuring the amount of fat in the pancreas is morphometric analysis, a computer assisted technique that exactly calculates the amount of pancreatic fat based on the area highlighted during micro scopy (39). Some evidence exists that pancreatic fat accumulation is unevenly distributed in the pancreas (with fatty replacement being more severe at the anterior aspect of the pancreas) and consequently sampling errors can occur during histological grading of pancreatic steatosis in pancreatic biopsies (40). with immunohistochemistry or electron microscopy, intracellular lipid accumulation can be shown in exocrine parenchyma and islet cells (12,32,41). Moreover, lee and colleagues (12) showed that intra cellular lipid accumulation precedes adipocyte infiltration. unfortunately, the current nomenclature for pancreatic fat accumulation makes no distinction in the accumulation of triglycerides in parenchymal or adipocytal tissue. Walters and coworkers (31) demonstrated that leukocyte infiltration accompanies pancreatic steatosis. However, Mathur *et al.(*25) and our study group7 were not able to reproduce these findings.

Imaging techniques

As histological examination requires a biopsy, pancreatic steatosis is most often found using imaging techniques. using ultrasonography, steatosis in the pancreas presents as a hyperechogenic pancreas (11,42). It must be kept in mind that, especially in obese patients, the pancreas is not always (completely) visible with abdominal ultrasonography techniques. Furthermore, pancreatic fibrosis is also hyperechogenic on abdominal ultrasonography, which virtually excludes this imaging technique as a screening tool for lipid deposition in the pancreas (42,43). When ultrasonography is applied for the detection of pancreatic steatosis, the kidney or the liver can be used as reference point; an echogenity of the pancreas higher than the liver or kidney could indicate pancreatic steatosis, while an echogenity similar to retroperitoneal fat implies the highest amount of pancreatic steatosis (44,45).

A complete steatotic pancreas will show as having the same density as adipose tissue using abdominal CT (14). The amount of pancreatic steatosis on CT can be measured using Hounsfield units, correlated to the spleen. as a steatotic pancreas will be hypodense on CT images (Figure 2), the amount of Hounsfield units compared to the spleen will be negative. No cutoff points for pancreatic steatosis on CT have been defined yet. The CT scan can be performed with or without intravenous contrast (46,47) and exposure to radiation with this technique hampers its use in research.

Several MRI methods are capable of measuring lipids in the pancreas, such as in-phase, opposed-phase and spectral– spatial excitation techniques (15,48). On T1weighted and T2weighted sequences, a steatotic pancreas will show as being (slightly) hyper intense compared with the liver (49), while opposed-phase sequences show a reduction in signal intensity in steatotic pancreases (47,50). Short time inversion recovery (stir)weighted sequences will retrieve a value of null in steatotic pancreases (a null value in stir-weighted sequences is characteristic of fat) (49).

With the use of magnetic resonance spectroscopy (MRS), the amount of ectopic triglycerides can be quantified noninvasively (13). In 2010, Lee and colleagues (12) showed an almost identical distribution of triglycerides in the exocrine and endocrine pancreas. MRS measurements of triglycerides in the whole pancreas can therefore be used as a surrogate marker for islet triglycerides. Furthermore, Hu *et al.*(51) reported that the three-dimensional Iterative Decomposition with echo asymmetry and least squares estimation (IDEAL)MRI method was superior to MRS in the measurement of pancreatic fat (51).

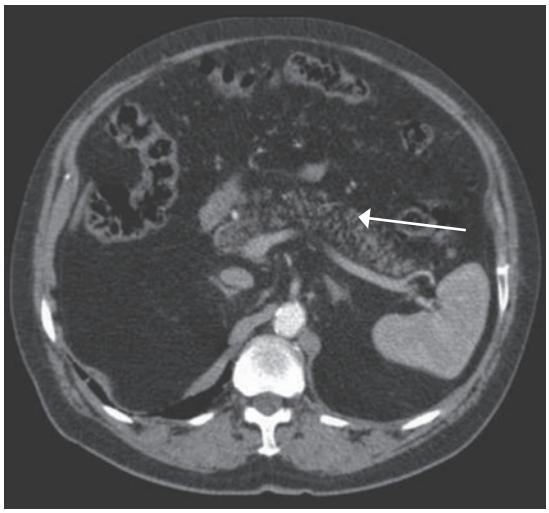

Figure 2 CT scan of pancreatic steatosis

A steatotic pancreas (arrow) will appear hypodense compared with the spleen (arrowhead) on CT scan images. Courtesy of T. L. Bollen, St Antonius Hospital, The Netherlands.

Using endoscopic retrograde cholangiopancreatography, severe pancreatic steatosis can present with ductal obstruction that resembles pancreatic carcinoma (52). However, pancreatic steatosis can be distinguished from pancreatic carcinoma by its abrupt obstruction in the main pancreatic duct with smooth tapering (52).

Although CT and MRI are useful techniques for detecting pancreatic steatosis, their use is hampered by lack of research, and the detection limit for pancreatic steatosis using these methods is unknown. Additionally, no papers reported cutoff points for clinical symptoms, or sensitivity and specificity for the detection of pancreatic steatosis with these imaging techniques. Future research must focus on these matters and comparative trials are needed to conclude which technique is superior for detecting pancreatic steatosis. For now, the 'gold standard' for detecting pancreatic steatosis remains histology and biochemical measurements, but MRS is almost equivalent to histology and biochemical measurements for *in vivo* use.

ETIOLOGY

As mentioned in the introduction, obesity is strongly associated with pancreatic steatosis (8–10,25,44,53–57). Obesity results in adipocytes infiltrating the pancreas

(32). Moreover, increasing age has been associated with an increase in the levels of pancreatic steatosis (9,39). In childhood and adolescence the amount of fat increases linearly with the volume of the pancreatic parenchyma (39). However, in adulthood the amount of fat increases independently of the amount of pancreatic parenchyma. Obesity and age are not the only causes of pancreatic steatosis. various syndromes and diseases are associated with the disease, as discussed below.

Congenital syndromes

Pancreatic fat replacement has been associated with a number of congenital syndromes, such as cystic fibrosis (18,58–69), shwachman–Diamond syndrome (49,70–74), Johanson–Blizzard syndrome (75), and heterozygous Carboxylesterlipase mutations (35). These syndromes also share pancreatic exocrine insufficiency as a symptom. in cystic fibrosis, mucous plugs obstruct the pancreatic ductules, thereby leading to damage and death of pancreatic parenchyma with subsequent exocrine dysfunction. It has been hypothesized that the empty spaces are then filled up with adipocytes (31). In the other congenital syndromes
the cause of pancreatic steatosis is still unknown.

hemochromatosis

In hemochromatosis, iron overloading occurs in the cells of the reticuloendothelial system. When the iron storage capacity of the reticuloendothelial system reaches its limit, iron is stored in the parenchyma of other organs (most often in the heart, liver, skin and endocrine organs such as the pancreas). Iron overload in the pancreas causes exocrine and endocrine dysfunction, pancreatic fibrosis and fat replacement (76). Lin *et al.(*17) have presented a patient with transfusion-dependent myelodysplastic syndrome who developed pancreatic fat replacement after numerous blood transfusions and consequent iron overload. This observation was confirmed by the development of pancreatic steatosis in patients with transfusion-dependent αthalassemia major (77,78). Iron overload has been hypothesized to cause fatal damage to the pancreatic parenchyma, which is replaced by adipose tissue (fatty replacement). Toxic agents or medications in many articles, the relationship between pancreatic steatosis and Cushing syndrome or steroid therapy is stated (26,31,52,79). However, no statistical analysis was performed in the original 1966 paper by Walters (31) that identified severe pancreatic steatosis in patients who were treated with cortisone or its analogues. In a case report, Makay *et al.(*19) presented an individual with pancreatic steatosis after neoadjuvant chemotherapy with gemcitabine. Additionally, in 2009, rosiglitazone has been shown to exacerbate pancreatic fat infiltration (80).

Other factors

Pancreatic fat replacement is related to pancreatic duct obstruction and can be induced by viral infections (for example, infection with reoviruses) (16,31,81,82). Duct obstruction leads to necrosis of the acinar cells, with fat replacement within 48 h. Hepatic disease has also been suggested to be a cause of pancreatic steatosis (26,37,79). Currently, only case reports of patients with chronic hepatitis B and liver cirrhosis underpin this hypothesis (31,36,83). Furthermore, pancreatic steatosis has been associated with malnutrition and has been observed in a patient with kwashiorkor (84). However, its clinical relevance in association with this form of malnutrition is unknown. In patients with AIDS, pancreatic steatosis can also be found in association with low BMI, hypo-albuminosis and acinar atrophy (85). Chehter and colleagues (85) hypothesized that AIDS leads to protein-energy malnutrition, which then leads to pancreatic changes, as seen in individuals with kwashiorkor.

CLINICAL CONSEQUENCES

Metabolic syndrome and diabetes mellitus

Obesity is associated with the metabolic syndrome (or syndrome X), which consists of hypertension, low plasma HDl cholesterol levels, hypertriglyceridemia, impaired glucose regulation and abdominal obesity (86). Obesity also causes fat infiltration of organs such as the liver, striated muscle, heart and pancreas (6). Consequently, NAFLD is strongly associated with the metabolic syndrome, and some clinicians suggest that it must be part of the definition of this disorder (87). This suggestion is supported by the fact that pancreatic steatosis, related to obesity, is associated with the metabolic syndrome (44) and NAFLD (7).

The association of insulin resistance with the metabolic syndrome is the cornerstone of the pathogenesis of type 2 diabetes mellitus. Type 2 diabetes mellitus occurs when pancreatic β cell dysfunction leads to impaired nsulin secretion in the context of insulin resistance (88).

The pathogenesis of β cell dysfunction is still unclear, but glucotoxicity and lipotoxicity have been proposed to have a role (for more information see the review by van Raalte *et al.*89). In animal models, triglyceride overload in pancreatic β-cells leads to lipotoxicity and lipoapoptosis (90). The increased pancreatic triglyceride levels observed in NAFPD have been hypothesized to reflect an increased amount of triglycerides in pancreatic β cells, which then causes β cell dysfunction (12). Another hypothesis is that intrapancreatic adipocytes have a negative paracrine effect on β cells. However, one can also postulate that NAFPD and type 2 diabetes mellitus are both just consequences of obesity, and that NAFPD is not involved in the pathogenesis of type 2 diabetes mellitus.

Pancreatic steatosis is present in the prediabetic phase and the amount of pancreatic fat increases before type 2 diabetes mellitus occurs (12,13). Moreover, in patients with impaired fasting glucose and impaired glucose tolerance, pancreatic fat is negatively associated with insulin secretion (P <0.03), which suggests that β cell Dysfunction is present in these individuals (55). This finding was confirmed by Tushuizen *et al.*29 who found a negative correlation between NAFPD and β cell function in nondiabetic individuals (P <0.01) (29). A notable relationship between NAFPD and diabetes was not observed, a finding that has been confirmed by Saisho and colleagues (39). Moreover, data from van der Zijl and coworkers shows no relationship between NAFPD and hyperglycemic clamp-derived secretion parameters (91,89). In their 2010 review, van Raalte *et al.*89 conclude that current evidence suggests that pancreatic steatosis is innocuous and is probably not a cause of lipotoxicity in pancreatic β cells (89), a conclusion shared by Szendroedi and colleagues (92). We agree with these researchers that there is insufficient evidence available to define a causal relationship between NAFPD and type 2 diabetes mellitus— the inactive role of naFPD in the pathogenesis of type 2 diabetes mellitus is still to be proven, or indeed refuted, by further research.

Exocrine dysfunction

It is widely known that >90% of pancreatic exocrine tissue must be destroyed before exocrine dysfunction occurs (93). In 1976, Savvina concluded that even massive pancreatic fat replacement (only 10% of exocrine parenchyma remaining) does not cause exocrine dysfunction (94). By contrast, Dupont *et al.(*95) hypothesized that the reduction of pancreatic enzymes is an early phenomenon in pancreatic lipomatosis. the researchers stated that pancreatic lipomatosis is the second most common cause of pancreatic insufficiency in childhood. Indeed, in a few childhood syndromes (cystic fibrosis, shwachman– Diamond syndrome and Johanson–Blizzard syndrome) exocrine dysfunction and pancreatic steatosis often coexist, as described earlier. The literature on exocrine dysfunction in pancreatic steatosis is scarce, apart from a few case reports; no series have been reported (14,78,96,97).

More research considering the degree and influence of pancreatic steatosis on the exocrine pancreas is therefore needed. If exocrine dysfunction occurs, patients present with chronic diarrhea, fatty stools, weight loss and/or general symptoms of malabsorption. Furthermore, imaging studies have reported a pancreas completely replaced by fat (14,78,96,97).In theory, fat droplet accumulation in acinar cells could cause exocrine insufficiency in pancreatic steatosis (12,32,41). However, to date, this mechanism has not been confirmed. Pancreatic adipocytes could have negative paracrine effects on acinar cells, thereby decreasing the exocrine function

of acinar cells. On the other hand, pancreatic steatosis could result from an underlying disease causing death of acinar cells and subsequent fatty replacement, which eventually could lead to pancreatic exocrine insufficiency.

Acute pancreatitis

Obesity is related to the severity of acute pancreatitis (98,99). Zyromski and colleagues(100) showed that obese mice develop more severe pancreatitis after cerulean hyperstimulation than lean mice. Furthermore, obesity is associated with developing organ failure,(101) local complications,(102) a longer hospital stay (103) and even increased mortality in patients with pancreatitis (99,104). Frossard and coworkers(105) defined five hypotheses regarding the causal relationship between obesity and acute pancreatitis. One hypothesis is that hepatic dysfunction associated with obesity might enhance the systemic inflammatory response. Another hypothesis is that pancreatic microcirculation in obese patients is reduced, increasing the risk of ischemic injury. Also, obesity restricts the inspiratory capacity, leading to ventilation or perfusion mismatch and subsequent hypoxemia. Another link between obesity and acute pancreatitis could be that necrosis and inflammation is often located in pancreatic fat. When the amount of pancreatic fat increases because of obesity, it is reasonable to postulate that the severity of an attack of acute pancreatitis would subsequently increase. of interest is the hypothesis that the increased amount of pancreatic fat (NAFPD) associated with obesity causes a more severe episode of acute pancreatitis. Adipose tissue can be regarded as an endocrine organ, secreting adipokines, chemokines and cytokines (collectively called adipocytokines) (106). In obesity, an imbalance in these adipocytokines causes a general inflammatory state (106,107) and this imbalance in hormone levels has been associated with NAFLD and atherosclerosis (106,108). It is plausible that pancreatic adipocytes could introduce an inflammatory milieu in the pancreas, making this organ more susceptible to pancreatitis. In support of this hypothesis, an increased amount of pancreatic toxic fats and inter leukin 1αand tumor necrosis factor (cytokines that are associated with the initiation of pancreatic inflammation) (109) has been observed in obese mice (25,100). The condition of pancreatitis owing to NAFPD has been termed non alcoholic steatopancreatitis (NASP) by Pitt and his group (25,110). This concept is analogous to the development of NASH in patients with NAFLD. Currently, our group is employing a CT-based study to elucidate a relationship between pancreatic steatosis and the severity of acute pancreatitis. Preliminary data in a patient population with predicted severe acute pancreatitis ($n = 105$) demonstrates a significant relationship between pancreatic steatosis (measured as pancreatic Hounsfield units corrected by the splenic Hounsfield units) and Ct severity index ($P < 0.03$; van Geenen and Bollen, unpublished work).

Pancreatic cancer

Obesity has been associated with multiple types of cancer, such as endometrial, renal cell, breast, colon and esophageal cancer (5,111,112). Evidence that obesity is also linked to pancreatic cancer is increasing (113,114), as pancreatic steatosis is related to obesity, NAFPD has been hypothesized to be involved in the development of pancreatic cancer (25). Zyromski and colleagues (115) have shown that the adipocyte mass is markedly greater in pancreatic tumors of obese mice than in lean mice. This observation has been confirmed in human pancreatic cancer (H. a. Pitt, unpublished work). These data suggest a role for pancreatic adipocytes in the development of pancreatic cancer. NAFPD has also been suggested to cause pancreatic cancer via NASP, a concept analogous to NAFLD, which can cause hepatic cancer via NASH and hepatic cirrhosis. Various investigators are convinced that pancreatic steatosis is associated with chronic pancreatitis, however, no original article to support this relationship can be found (26,52,96).

Most patients with pancreatic cancer have substantial pancreatic fibrosis. However, whether this pancreatic fibrosis has been caused by NASP, after which pancreatic cancer develops, or whether pancreatic cancer causes the fibrosis owing to duct obstruction is unknown. We believe there is insufficient evidence to support the theory of NASP as a precursor of pancreatic adenocarcinoma. In patients with pancreatic cancer, pancreatic steatosis promotes dissemination and increases the lethality of the disease (30). Also, it has been theorized that duct obstruction associated with pancreatic cancer can cause pancreatic steatosis (116–119). Evidence to support this theory was presented by Walters in 1966 in a study on 40 rats (31).

Pancreatic fistula

The risk of developing pancreatic fistula after pancreatoduodenectomy is increased when the pancreatic consistency is soft (37). Mathur *et al.(*38) were the first to report a study on the relationship between pancreatic steatosis and pancreatic fistula. In their retrospective case– control study, they found that presence of pancreatic fat significantly increased the risk of developing pancreatic fistula (P <0.001). These findings were confirmed by later studies (54,56,120). One study showed that individuals with 10% fatty tissue in the pancreas have significantly increased risk of developing pancreatic fistula (P <0.0003) (56). Whether pancreatic steatosis causes this increase in pancreatic fistula by softening the pancreatic tissue is unclear. Lee *et al.(*120) concluded that pancreatic consistency is related to the amount of pancreatic fat. However, other studies found pancreatic consistency to be related to pancreatic fibrosis and not pancreatic fat (54,56). Moreover, 2010 data conclude that pancreatic steatosis is a more reliable risk factor for the development of pancreatic fistula than a soft pancreas (54).

Pancreatic transplantation

In pancreatic transplantation, obesity of the transplant recipient increases the risk of dehiscence, intra-abdominal infection and gangrene, but does not influence allograft failure (121). Obesity in the transplant donor increases the risk of technical surgical failure, but in successful transplantations the risk of allograft failure is unchanged (122). In 2004, Nghiem *et al.(*123) 'defatted' a pancreas of a donor with a high BMI and transplanted it successfully. This intervention could potentially reduce the amount of technical failure observed during pancreatic transplantation. in addition, isolation of pancreatic islet is a technique used in islet transplantation, and a high BMI and pancreatic steatosis has been shown to increase the yield of islet isolation (124,125).

Pancreatic hyperenzymia

In an unknown disorder called 'pancreatic hyperenzymia', hypersecretion of pancreatic enzymes in the absence of pancreatic disease exists.126,127 Cavallini and colleagues(126) describe a relationship between pancreatic steatosis (hyperechogenic pancreas on ultrasonography) and hyperamylasia in their study population. However, in a MRI-based study, no relationship between hypersecretion of pancreatic enzymes and pancreatic steatosis was demonstrated (127).

CONCLUSIONS

Many different terms to describe pancreatic fat accumulation are used interchangeably. Uniform definitions regarding different forms of pancreatic fat accumulation are needed to aid the comparison and design of future studies. We propose to use pancreatic steatosis as a general term for pancreatic fat accumulation; the term NAFPD must be reserved for fat accumulation in association with obesity. Pancreatic fatty replacement is an adequate term for when acinar death leads to replacement with adipocytes in the pancreas. In pancreatic fat replacement, pancreatic steatosis is probably an 'innocent bystander'. this scenario is most likely the case in pancreatic exocrine dysfunction, hemochromatosis, viral infection and some congenital syndromes (Figure 3). in pancreatic fat infiltration (owing to obesity, also called naFPD), the role of pancreatic steatosis is less clear. NAFPD has been suggested to have a role in type 2 diabetes mellitus, acute pancreatitis, pancreatic cancer and the formation of pancreatic fistula after pancreatic surgery (Figure 3). Unfortunately, current evidence to support these theories is insufficient. Future research must focus on pancreatic steatosis, and NAFPD in particular, to examine the multiple associations and underlying pathophysiology of these diseases.

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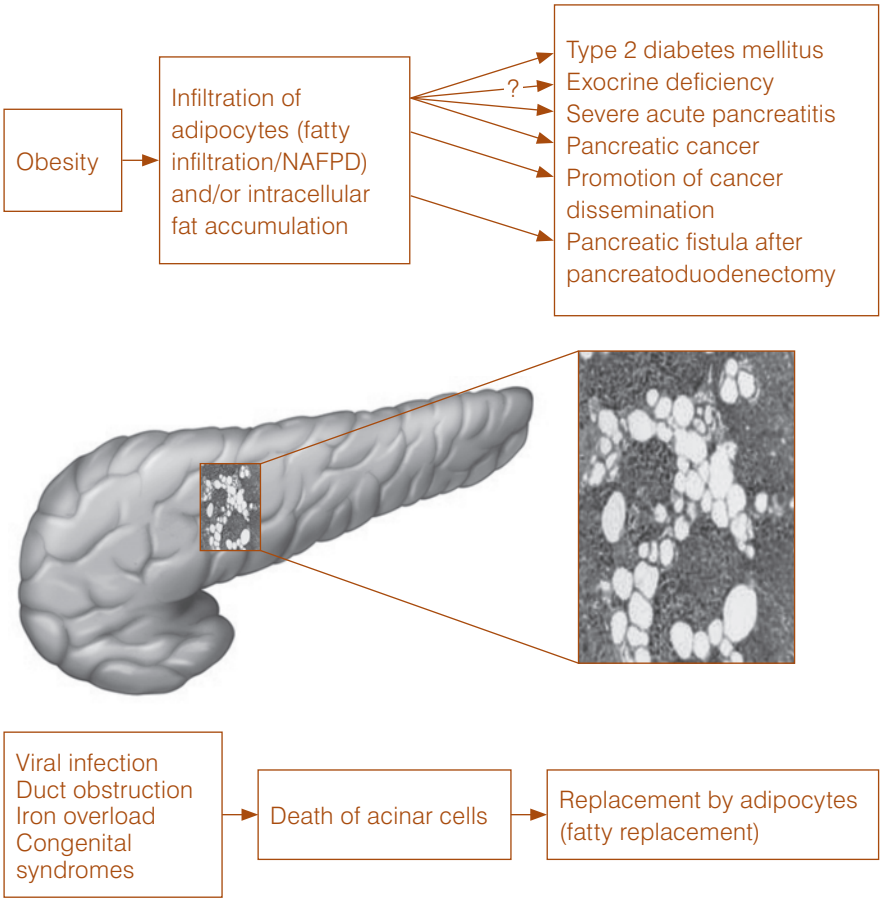

Figure 3 Etiological factors and consequences of pancreatic steatosis

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List of abbreviations

BMI	Body mass index
C.I	Confidence interval
CRF	Case record file
CRP	C-reactive protein
CTSI	CT-severity index
CT	Computer tomography
ERCP	Endoscopic retrograde cholangiopancreatography
HC	Hip circumference
HR	Hazard ratio
ICU	Intensive care unit
i.e.	id est
Kg	Kilogram
Lat	lateral
M	meter
NASH	Non-alcoholic steatosis hepatis
OR	Odds ratio
s.c.	subcutaneous
VAT	Visceral adipose tissue
v-d	ventral-dorsal
WC	Waist circumference
WC_{BMI}	Calculated WC, corrected by BMI
W/H	Waist to hip ratio

CHAPTER 8

THE "OBESITY PARADOX" IN PREDICTED SEVERE ACUTE PANCREATITIS

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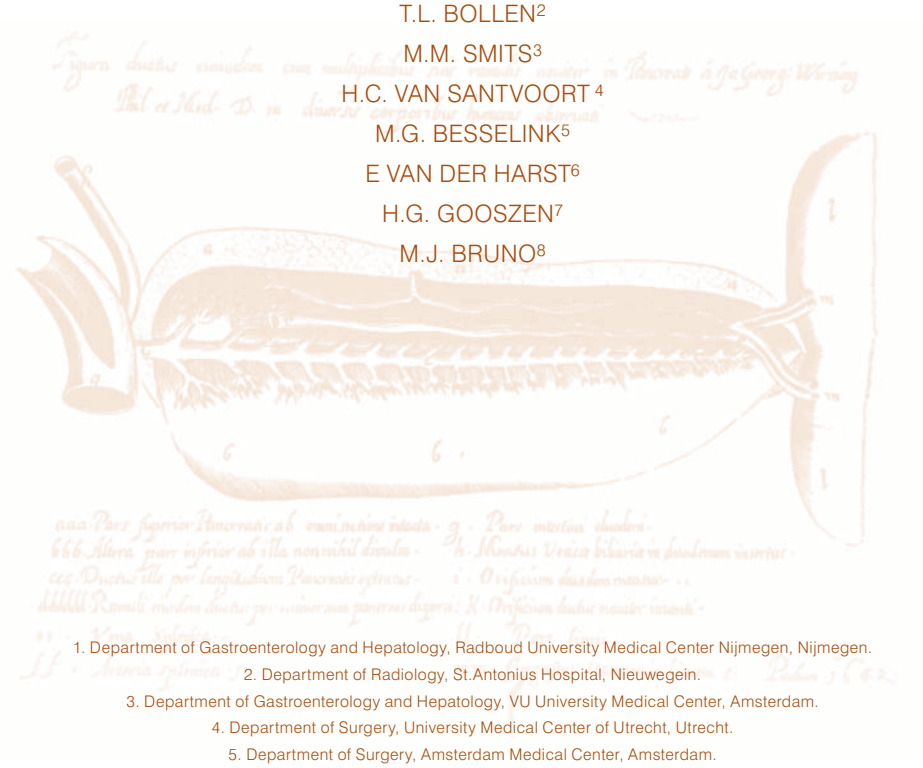

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On behalf of the Dutch Pancreatitis Study Group

Submitted

ABSTRACT

Introduction: Obesity is widely regarded as a risk factor for poor outcome in acute pancreatitis. Indeed, several recent meta-analyses on obesity in acute pancreatitis show an increased relative risk for local complications, systemic complications, and death, but did not take into account the predicted severity of disease. In several conditions, other than pancreatitis, a so called "obesity paradox" has been described meaning that certain subgroups of obese patients in fact have an improved outcome. In the current study we examined whether the obesity paradox exists in acute pancreatitis and (central) overweight/obesity, is associated with an increased risk of complications and mortality in patients with predicted severe acute pancreatitis.

Methods: In the current post-hoc analysis of a observational, multicenter study we included patients with a primary episode of predicted severe acute pancreatitis from a larger cohort of patients enrolled in a previous randomized clinical trial. Criteria for predicted severe acute pancreatitis were based on APACHE score ≥8, or Imrie score ≥3, or CRP >150 mg/L within 72 hours after onset of symptoms. The primary endpoint was mortality. Secondary endpoints were morbidity and intensive care unit (ICU)-admission. Anthropometric assessment included body mass index (BMI), CT measurements including hip and waist diameters /circumferences (WC), and calculation of the WC/BMI.

Results: 144 patients with predicted severe acute pancreatitis were evaluated. Multivariable analysis showed an association between mortality and high WC/BMI (OR 10.0, 95% C.I. 1.89-52.7), and a lower BMI (OR 0.84, 95% C.I. 0.71-0.99). For morbidity, multivariable analysis showed an association with a higher WC/BMI (OR 11.5 95% C.I. 2.07-63.8), CTSI (OR 9.81, 95% C.I.: 3.22-29.2) and a lower BMI (OR 0.79, 95% C.I.: 0.66-0,94).

Conclusion: This is the first study to show that the "obesity paradox" also exists in patients with predicted severe pancreatitis; obese patients suffering from a predicted severe attack of acute pancreatitis have a better outcome than non-obese patients, unless a patient has central obesity.

INTRODUCTION

The prevalence of overweight and obesity is increasing rapidly worldwide. In 1996, 13.3% of the US population had a body mass index (BMI) of >30. In 2005, this already doubled to nearly 25% [1]. In Europe, overweight affects 30-70% of the adult population and 10-30% is obese[2]. In China the prevalence of overweight and obesity in children and adolescence increased from 1992 to 2002 by 22.8 and 7.1%, respectively[3]. Traditionally, overweight is defined as a body mass index (BMI) > 25 kg/m^2 and obesity by a BMI >30kg/m (WHO-definition) [2].Overweight and obesity are major risk factors for a wide range of chronic diseases, among them metabolic syndrome, NASH, type II diabetes, cardiovascular disease, and various cancers including colorectal, breast and pancreatic cancer[4].
Increasing evidence indicates that central obesity (or abdominal adiposity) is a better predictor than BMI in predicting the outcome of cardiovascular disease and several metabolic abnormalities[4-7]. Alternative measurements of obesity, focusing on central obesity are: waist circumference (WC), waist/hip ratio (W/H), waist/height ratio and intra-abdominal fat-area[8]. Recent studies have shown that WC adjusted for BMI is strongly and positively associated with overall mortality[9]. It has been suggested that adjusted-WC acts as a surrogate measure for intra-abdominal fatness[10].

Obesity has long been regarded as a risk factor for poor outcome in severe acute pancreatitis. Indeed, several recent meta-analyses on obesity in acute pancreatitis showed a relative risk of 4.3 for local complications, 2.0 for systemic complications, and 2.1 for death [11-15]. However, the incidence of acute pancreatitis is increased in obese patients and hence results in a proportional increase and relative over-representation of obese patients with acute pancreatitis[14]. In the aforementioned meta-analyses no stratification was applied with regard to the predicted severity of acute pancreatitis, which is associated with an increased mortality. However, in several conditions, other than pancreatitis, a so called "obesity paradox" has been described meaning that certain subgroups of obese patients in fact have an improved outcome[16-19]. In the current post-hoc analysis of a large observational multicenter study, we examined whether (central) overweight/obesity, is associated with an increased risk of complications and mortality in patients with predicted severe acute pancreatitis.

METHODS

Study population and design

This study evaluated a subset of patients with predicted severe acute pancreatitis from a larger cohort of patients enrolled in the Dutch randomized clinical trial on probiotic prophylaxis in acute pancreatitis: the PRObiotics in PAncreatitis TRIAl (PROPATRIA)[20]. For this observational study an experienced abdominal radiologist peformed additional abdominal CT-measurements on existing PROPATRIA study CT sets including hip and waist diameters (and calculated hip and waist circumferences), ventral and dorsal subcutaneous fat layer, Hounsfield measurements of the liver, spleen and pancreas.

The PROPATRIA study included adult patients with a primary episode of predicted severe acute pancreatitis of all causes. Acute pancreatitis was defined as abdominal pain with serum amylase and/or lipase levels elevated to at least three times the institutional upper limit of normal. Criteria for predicted severe acute pancreatitis were: a) an Acute Physiology, Age and Chronic Health Evaluation (APACHE)-II score ≥8[14], or b) Imrie score ≥3[15], or c) C-reactive protein (CRP) >150 mg/L[16] within 72 hours after onset of symptoms. Between March 2004 and March 2007, 296 consecutive patients with predicted severe acute pancreatitis were enrolled in 8 university medical centers and 7 major teaching hospitals. The current observational study included patients from PROPATRIA diagnosed with acute pancreatitis from March 2004 till March 2006. Exclusion criteria were: 1. No digital abdominal CT-scan available (inaccurate anthropometric measurements), 2. incomplete abdominal CT-scans (pelvic region not included), 3. no acute pancreatitis (alternative diagnosis).

Treatment protocol

Patients were treated according to a fixed treatment protocol[20]. This consisted of nasojejunal enteral feeding with a probiotic preparation or placebo according to treatment allocation, administered within 72 hours after onset of symptoms for a maximum of 28 days. Antibiotic prophylaxis in necrotizing pancreatitis was not allowed. Physical examination and laboratory measurements were performed daily. Contrast-enhanced CT was performed routinely 7-10 days after admission, and the CT-severity index was determined[21]. Patients with infected necrotising pancreatitis were treated with percutaneous drainage and/or operative intervention according to decision of the treating physician. In case of acute biliary pancreatitis (defined in a former study)[22], the decision to perform endoscopic retrograde cholangiopancreatography (ERCP), with or without papillotomy, was left to the treating physician.

Endpoints

The primary and secondary endpoints were mortality and overall complications during admission and 90-day follow-up after admission (Box1). All complications were weighted equally; multiple complications in the same patient were considered as one endpoint. Organ failure was defined asPaO2 <60 mmHg despite FiO2 of 30%, or the need for mechanical ventilation (pulmonary insufficiency); serum creatinine >177 mmol/L after rehydration or need for hemofiltration or hemodialysis (renal failure), and systolic blood pressure <90 mmHg despite adequate fluid resuscitation or need for vasopressor support (cardio circulatory insufficiency), adapted from the Atlanta classification[23]. Multi-organ failure was defined as failure of two or more organ systems on the same day. Secondary endpoints were intensive care unit (ICU)-admission and ICU-admission time.

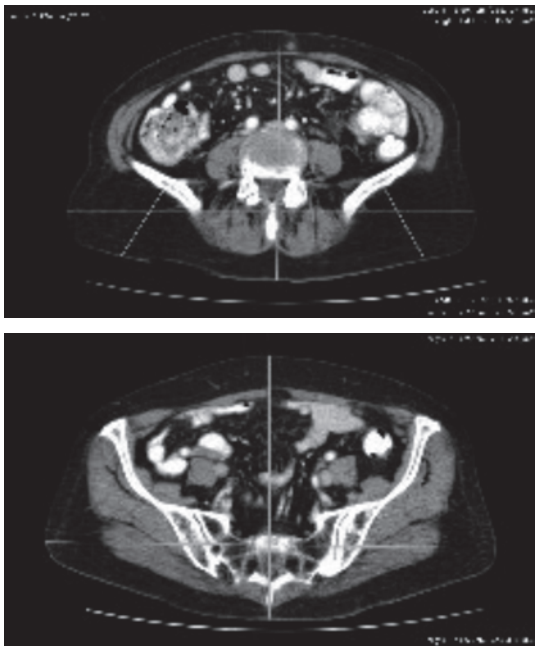
Box 1 Definitions of complications included in endpoint and overall complications

- **Pancreatic necrosis**: pancreatic non-enhancement on contrast enhanced CT scan performed 7-10 days after admission.
- **Infected pancreatic necrosis**: positive fine needle aspiration culture of peripancreatic fluid or positive culture of necrosis removed during first surgical intervention.
- **Bacteremia**: positive blood culture: for bacteria that are usual non-pathogens like coagulase-negative staphylococci at least two samples had to be positive.
- **Infected ascites**: bacteria detected in aspirate of intraperitoneal fluid or abdominal fluid sampled during surgical exploration.
- **Pneumonia**: coughing, in combination with dyspnea, chest film showing infiltrative abnormalities, or lowered arterial blood gas with positive sputum culture. If on the intensive care unit a positive endotracheal culture is mandatory.
- **New onset organ failure**: initial (for the first time) onset of organ failure.

Anthropometric measurements

Patients' weight and height were noted on admission**.** The body mass index (BMI) was calculated as: the patients' weight/(height)^2 in kg/m^2. Anthropometric measurements were performed on transverse slides of abdominal CT-scans at two regions: the waist (umbilical level) and hip (spina iliaca anterior superior level or anterior superior iliac spine) (Fig 1a and b). In order to estimate the waist and hip circumference (WC

and HC), the shape of a cross-sectional plane of the body was considered an ellipse by approximation. The circumference at the waist and hip regions were respectively determined at the umbilical and the spina iliaca superior anterior levels.

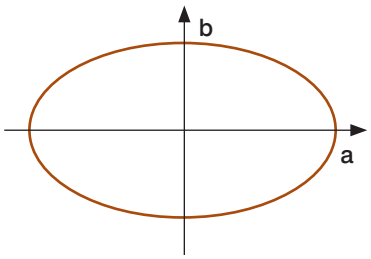


a Umbilical region

b Anterior superior iliac spine region

Figure 1 Anthropometric measurements (**a** and **b**)

The lateral and ventral-dorsal diameters were measured at the waist and hip region. The circumference of the waist and hip was calculated by approximation by the first formula of Ramanujan (1914), a simplification of a first degree integral (Figure 2). The waist to hip ratio (W/H) was subsequently determined by the calculated waist-circumference (WC) divided by the calculated hip circumference (HC). WC adjusted for BMI (WC_{BMI}) is calculated as WC minus the calculated WC (WC_{calc}), or mathematically: $WC_{BMI} = WC - WC_{calc}$. The WC_{calc} is determined via linear regression of the WC versus the BMI in the study population[10]. An alternative WC adjusted for BMI is introduced by our study group in order to obtain a more practical parameter to accurately estimate intra-abdominal fatness. This parameter is calculated by the WC to BMI ratio ($cm/kg/m^2$). The WC/BMI and BMI were divided into 4 percentiles: 0-25%, 25-50%, 50-75% and 75-100%. Each group was analyzed and mortality rates were compared to the remainder groups. The ventral and dorsal subcutaneous (s.c.) fat layers were measured para-umbilical at the waist in cm (figure 1a and b).



Ramanujan's first approximation formula:
P=π [3(a+b)-√(3a+b)x(a+3b)]

P = circumference
a = radius of longest radius (1/2 x diameter)
b = radius of shortest radius (1/2 x diameter)

Figure 2 Circumference calculation of an ellipse

Data collection

Local physicians completed the case-record forms prospectively. An independent data monitor performed an onsite cross-check of at least 10% of the individual patient data. One experienced radiologist (TLB) and gastroenterologist (EVG), blinded for treatment and clinical outcome, reevaluated all CTs for the presence and extent of pancreatic necrosis, CT-severity index (CTSI) and anthropometric measurements. Before any analysis and blinded for treatment, two investigators (HCvS and MGHB) checked all data on baseline characteristics and primary or secondary endpoints with primary source data. Analyses were performed only after agreement was reached on all endpoints.

Statistical analysis

Analyses for the current study were performed according to a pre-established analysis plan using SPSS version 17.01 (SPSS, Chicago, IL, USA).
Continuous data are presented as mean (±SD) and in case of skewed distributions as median (range). Univariable analysis of continuous variables was performed with binary logistic regression and logistic regression (ANOVA). Proportions were compared by the Fisher's exact test. Multivariable logistic regression analysis was used to adjust for possible confounders. All baseline variables with a p-value smaller than 0.200 were entered in a model as covariables. Backward stepwise regression was used to exclude variables with $P > 0.05$.

RESULTS

A total of 211 patients with predicted severe acute pancreatitis were evaluated for inclusion. Sixty-seven patients were excluded because of an alternative diagnosis (n=3), incomplete abdominal CT-scans (n=4), or hardcopy abdominal CT-scan only (n=60), leaving 144 patients for final analysis (Figure 3). The anthropometric

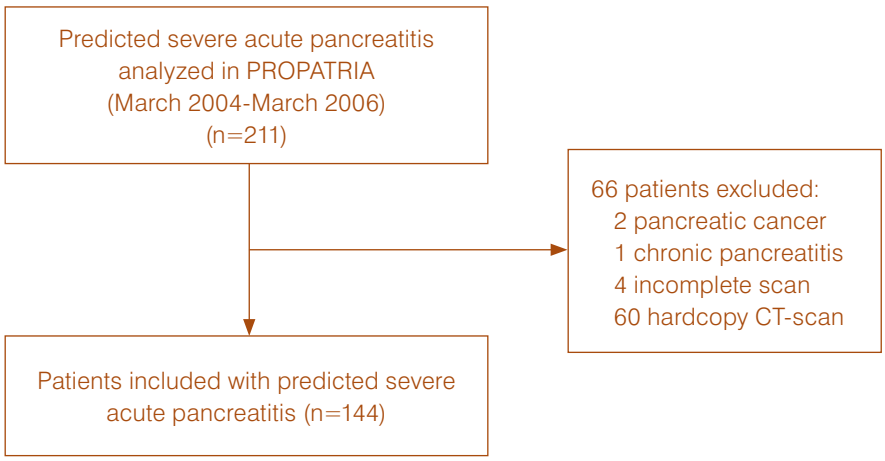


Figure 3 Patient inclusion flowchart

data, etiology, age and sex are listed in table 1. The BMI was not noted in 32 patients. From this missing group, 8 patients died, resulting in a mortality of 25%. In 7 patients the hip region was not scanned. Linear regression of the WC (in cm) and BMI (in kg/m^2) resulted in the following equation in our population: calculated WC (WC_{calc}) = 1.719 x BMI +53.36. The WC corrected for BMI (WC_{BMI}) was calculated by the equation: WC_{BMI} = WC – (1.719 x BMI + 53.36).

Morbidity

The different complications and their relation with anthropometric parameters are listed in table 2. The CTSI and WC/BMI were significantly related to the overall morbidity in patients with predicted severe acute pancreatitis (OR 5.31, 95%C.I.: 2.74-10.28 and OR 2.76, 95%C.I.:1.10-6.97) and to all complications including infectious complications, necrotizing pancreatitis, infected pancreatic necrosis, new onset organ failure and multiple organ failure. The ventral-dorsal umbilical waist diameter and WC/BMI are significantly related to new onset organ failure and multiple organ failure. The ventral-dorsal hip diameter and the ventral- dorsal umbilical waist diameter were significantly related to infected complications.

With multivariable logistic regression, the CTSI, BMI and WC/BMI were included. Separate multivariable analysis for BMI and WC/BMI were performed with the CTSI, since the WC/BMI and BMI are related. (Table 4). BMI showed an inverse relation to the morbidity rate (OR 0.79, 95% C.I.:0.66-0.94) whereas a higher WC/BMI and CTSI were significantly associated with higher morbidity rates (OR 11.5 and 9.81, 95%C.I.: 2.07-63.8 and 3.22-29.8).

Table 1 Patient characteristics

	Mean/ frequency	range	Standard deviation	Missing data	Percentiles (%) 1)<25, 2) 25-50 3) 50-75, 4) >75
Male (%)	59.7			0	
Age (year)	58.3	24-88	15.4	0	
Probiotics(%)	49.3			0	
BMI (kg/m^2)	28.3	16.5-51.4	5.77	32	<25, 25-26.8 26.9-30.7, >30.7
Mortality(%)	10.4			0	
Morbidity or mortality (%)	50.7			0	
Morbidity (%)	41.7			0	
CTSI (points)	4.64	0-10	2.54	0	
ICU admission (%)	29.9			0	
ICU admission (days)	4.95	0-89	13.39	0	
Biliary cause (%)	38.2			0	
Umbilical waist diameter v-d (cm)	27.876	18.0-47.4	4.52	0	
Umbilical waist diameter lateral (cm)	36.41	21.1-57.2	4.88	0	
Umbilical waist circumference (cm)	102.06	67.39-149.32	13.27	0	
WC/BMI (cm/kg/m^2)	3.67	2.01-4.98	0.45	32	<3.40, 3.40-3.68 3.69-3.93, >3.93
WC_{BMI} (cm)	0.01	-40.6-23.79	8.57	32	
Hip diameter v-d (cm)	27.3	18.3-41.3	4.06	7	
Hip diameter lateral (cm)	38.04	23.9-55.5	4.98	7	
Hip circumference (cm)	104.19	72.46-144.53	11.88	7	
Waist hip ratio (cm)	0.98	0.77-1.23	0.06	7	
Ventral s.c. fat (cm)	2.61	0.8-13.6	1.55	1	
Dorsal s.c. fat (cm)	6.18	2.6-11	1.62	0	

Mortality

Univariable analysis revealed four parameters significantly associated with mortality (Table 3). Among patients who used a probiotic 16.9% of them died compared with 4.1% in the placebo group (OR 4.75, 95%C.I.: 1.28-17.62). A higher CTSI and WC/

Table 2 Complications versus anthropometric parameters

Variable P-value OR (95% C.I.) Average: yes / no	Total complications/ morbidity	Infectious complications	Infected necrosis	New onset organ failure	Multiple organ failure	Pancreatic necrosis
Gender (m/f):%	0.774	0.218	0.501	0.139	0.211	0.355
Admission age	0.686	0.288	0.286	0.400	0.985	0.052
Probiotics (yes/no: %)	0.414	0.637	0.937	0.040 2.28 (1.03-5.07) 64.7% / 35.3%	0.015 3.0 (1.20-7.32) 70.3% / 29.6%	0.157
CTSI (points)	0.000 5.3 (2.74-10.28) 6.8 / 3.1	0.000 1.55 (1.31-1.83) 6.3 / 3.8	0.000 1.76 (1.44-2.16) 7.7 / 4.0	0.000 1.54 (1.30-1.83) 6.8 / 4.0	0.000 1.62 (1.35-1.94) 7.2 / 4.0	-
BMI (kg/m^2)	0.154	0.783	0.803	0.055	0.114	0.544
Biliary cause(yes/no: %)	0.469	0.206	0.819	0.416	0.458	0.145
Umbilical waist diameter v-d (cm)	0.713	0.038 1.09 (1.01-1.18) 29.0 / 27.3	0.109	0.028 1.10 (1.01-1.20) 29.4 / 27.4	0.017 1.12 (1.02-1.22) 29.8 / 27.4	0.218
Umbilical waist diameter lateral (cm)	0.708	0.406	0.385	0.583	0.787	0.914
Umbilical waist circumference (cm)	0.640	0.115	0.169	0.139	0.154	0.507

WC/BMI (cm/kg/m^2)	0.031 2.76 (1.10-6.97) 3.8 / 3.6	0.138	0.198	0.000 11.4 (3.0-43.5) 4.0 / 3.6	0.001 9.94 (2.4-36.8) 4.0 / 3.6	0.10
WC_{BMI} (cm)	0.210	0.022 1.07 (1.01-1.13) 2.7/ -1.3	0.043 1.07(1.001-1.14) 3.4 / -0.8	0.002 1.12 (1.04-1.21) 5.0 / -1.3	0.005 1.12 (1.03-1.21) 5.2 / -1.0	0.026 1.07 (1.01-1.13) 0.89 / -4.3
Hip diameter v-d (cm)	0.658	0.008 1.13 (1.03-1.24) 28.5 / 26.5	0.050 1.11 (1.00-1.23) 27.8 / 26.9	0.197	0.486	0.318
Hip diameter lat (cm)	0.512	0.888	0.972	0.280	0.206	0.706
Hip circumference (cm)	0.455	0.123	0.253	0.171	0.240	0.806
Waist hip ratio	0.928	0.083	0.382	0.247	0.383	0.549
Ventral s.c. fat (cm)	0.542	0.918	0.451	0.964	0.216	0.926
Dorsal s.c. fat (cm)	0.860	0.755	0.936	0.902	0.630	0.620

s.c. = subcutaneous
v-d= ventral-dorsal
OR = odds ratio
OR = odds ratio
C.I. = confidence interval
C.I. = confidence interval

Table 3 Mortality versus (anthropometric) parameters

Variable	Average mortality Yes / No	p-value	OR	95% C.I.
Gender (m/f)	10.5 / 10.3	0.982	0.99	0.33-2.94
Admission age (year)	65 / 57.4	0.082	1.03	1.00-1.07
Probiotics (%)	16.9 / 4.1	0.012	4.75	1.28-17.62
CTSI (points)	6.27 / 4.45	0.012	1.28	1.06-1.55
BMI (kg/m^2)	24.8 / 28.7	0.031	0.84	0.71-0.98
Biliary cause (yes/no)	12.4 / 7.27	0.332	1.80	0.54-5.96
Umbilical waist diameter v-d (cm)	28.8 / 27.8	0.621	1.03	0.92-1.14
Umbilical waist diameter lateral (cm)	37.0 / 36.3	0.400	1.05	0.94-1.17
Umbilical waist circumference (cm)	104.3 / 101.8	0.485	1.01	0.98-1.05
WC/BMI (cm/kg/m^2)	4.09 / 3.63	0.020	13.02	2.52-67.4
WC_{BMI} (cm)	4.18 / -0.45	0.081	1.08	0.99-1.17
Hip diameter v-d (cm)	27.6 / 27.2	0.696	1.03	0.90-1.17
Hip diameter lat (cm)	38.9 / 37.0	0.495	1.04	0.93-1.16
Hip circumference (cm)	106.1 / 104.0	0.529	1.01	0.97-1.06
Waist hip ratio	0.99 /0.98	0.274	0.004	0.000-82.9
Ventral s.c. fat (cm)	2.12 / 2.67	0.154	0.63	0.33-1.20
Dorsal s.c. fat (cm)	6.02 / 6.19	0.692	0.93	0.67-1.32

s.c. = subcutaneous
v-d= ventral-dorsal
OR = odds ratio
C.I. = confidence interval

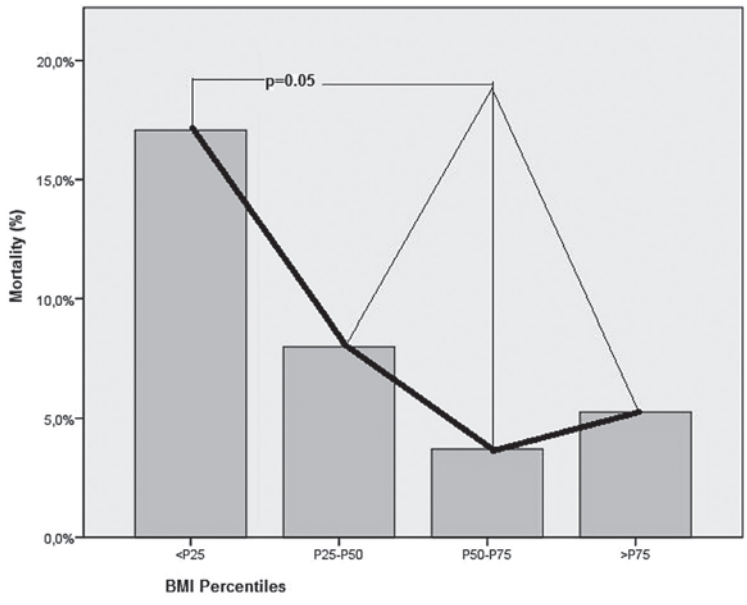
BMI were related to a higher mortality (OR 1.28, 95%C.I.:1.06-1.55 and OR 13.02, 95%C.I.:2.52-67.4). Additionally, a higher BMI was associated with a lower mortality (OR 0.84, 95%C.I.:0.71-0.98).

In the multivariable logistic regression the following parameters were included (univariable analyses $p < 0.200$): admission age, probiotics, CTSI-score, WC/BMI, BMI, WC_{BMI}, and s.c. ventral fat layer. Since the parameters WC/BMI and WC_{BMI} were directly related to the BMI, separate multivariable analyses for BMI, WC/BMI, WC_{BMI} and WC combined with BMI were performed (Table 4). A lower BMI and a higher WC/BMI were significantly associated with mortality (OR 0.84 and 9.97, 95%C.I: 0.71-0.99 and 1.89-52.7, Table 4). A separate insertion of the BMI and WC (instead of WC/BMI) in the multivariable logistic regression resulted in a significant relation of the two parameters with mortality (OR 1.1 and 0.70, table 4).

Table 4 Multivariable analysis on primary and secondary endpoints

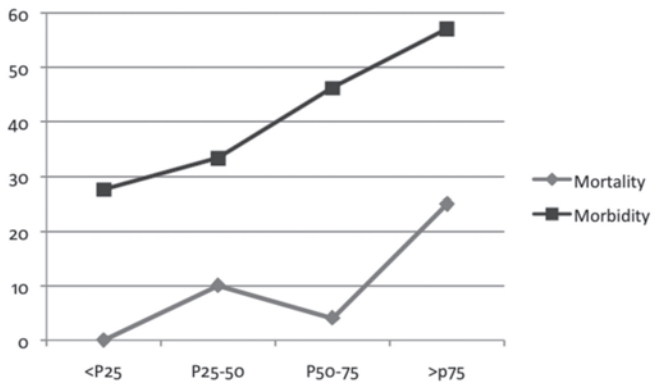
Endpoint	Variable	p-value	OR	(95% C.I.)
Morbidity	CTSI	0.000	9.81	(3.22-20.2)
	WC/BMI	0.005	11.5	(2.07-63.8)
	Separate analyses			
	BMI	0.008	0.79	(0.66-0.94)
	WC_{BMI}	0.193	1.07	(0.97-1.18)
Mortality	WC/BMI	0.007	10.0	(1.89-52.7)
	Separate analyses			
	BMI	0.039	0.84	(0.71-0.99)
	WC_{BMI}	0.077	1.08	(0.99-1.17)
	WC and BMI analysis			
	BMI	0.011	0.70	(0.53-0.92)
	WC	0.049	1.10	(1.00-1.20)

The BMI percentiles divided over 4 groups versus mortality are presented in Graph 1. The curve has an inverted J-shape, with a significantly increased mortality between the group 1 and the rest (0-25% percentile vs. 25-100%, P=0.05). For the WC/BMI



Graph 1 BMI percentiles versus mortality risk: inversed J-shape

these results are shown in Graph 2; patients in group 1 are less likely to die in predicted SAP (0% versus 13.3%, p=0.039), whereas patients in group 4 have an increased mortality rate compared to the rest of the groups (25% versus 4.8%, p=0.002).



Graph 2 WC/BMI percentiles versus morbidity and mortality risk

The x-axis contains the mortality rate (%) and the Y-axis contains the percentiles of WC/BMI.

ICU-admission and duration of stay

ICU-admission and duration of the ICU-admission (stay) were significantly related to an increased CTSI, ventral-dorsal umbilical waist diameter and WC_{BMI} (Table 5). A biliary cause of the acute pancreatitis was significantly protective against ICU-admission compared to a non-biliary cause (p=0.037; 23% versus 44%).

DISCUSSION

This to our knowledge is the first study to investigate the effect of the BMI and other anthropometric parameters on the course of an attack of predicted severe acute pancreatitis. The major findings of this study are: 1) a lower BMI is associated higher mortality and morbidity rates, and 2) a higher WC/BMI and WC are associated with higher morbidity and mortality rates. In other words: obese patients suffering from a predicted severe attack of acute pancreatitis have a better outcome than non-obese patients, unless a patient has central obesity.

In a recent meta-analysis including eight prospective studies, obesity (defined as BMI >30 kg/m^2) was associated with a significant increased mortality in patients

Table 5 ICU-admittance/stay versus anthropometric parameters

Variable	ICU-admittance P-value OR (95% C.I.) Average: yes vs no	ICU stay (days) P-value R^2 / F
Gender (m/f):%	0.138	0.062
Admission age	0.792	0.616
Probiotics (yes/no: %)	0.102	0.076
CTSI (points)	0.000 1.56 (1.32-1.85) 6.5 / 3.8	0.000 0.147 / 24.5
BMI (kg/m^2)	0.176	0.959
Biliary cause (yes/no: %)	0.037 0.46 (0.22-0.96) 23% / 44%	0.861
Umbilical waist diameter v-d (cm)	0.043 1.09 (1.003-1.177) 29.1 / 27.4	0.000 0.083 / 12.81
Umbilical waist diameter lateral (cm)	0.806	0.958
Umbilical waist circumference (cm)	0.244	0.082
WC/BMI (cm/kg/m^2)	0.007 4.36 (1.49-12.8) 3.87 vs 3.60	0.094
WC_{BMI} (cm)	0.021 1.07 (1.01-1.14) 3.15 / -1.14	0.003 0.077 / 9.19
Hip diameter v-d (cm)	0.181	0.084
Hip diameter lat (cm)	0.987	0.267
Hip circumference (cm)	0.499	0.113
Waist hip ratio	0.645	0.546
Ventral s.c. fat (cm)	0.892	0.958
Dorsal s.c. fat (cm)	0.907	0.511

with acute pancreatitis (OR 3.81; 95% C.I. 1.22-11.83) [13]. However, obesity was also associated with a significant increased predicted severity of the pancreatitis (OR 2.48; 95% C.I. 1.34-4.60). These findings suggest that in obese patients the incidence of predicted severe acute pancreatitis is increased, which in turn is associated with higher mortality. I n the aforementioned studies and meta-analysis however, predicted disease severity was not accounted for, which makes it

impossible to discern the true influence of obesity and/or abdominal fatness on morbidity and mortality.
The outcome of our multivariable analysis is in line with recent ICU-studies which found a relationship between increased BMI and decreased mortality. A recent meta-analysis[16] concluded that obesity in patients admitted to a ICU showed a trend towards a lower mortality, but longer hospital stay[16]. We could not confirm a relationship between BMI and ICU-stay. However, a significant relation between central obesity (WC_{BMI} and ventral-dorsal umbilical diameter) and the ICU-stay was found ($p=0.003$ and $p<0.001$, table 5). In a large ICU study, underweight was associated with an increased mortality (OR 1.19 95% C.I.: 1.08-1.32), whereas overweight, obesity and severe obesity was not associated with a significant increase or decrease in mortality[17]. A similar trend of decreased mortality in overweight patients compared with underweight and normal weight patients was reported in studies concerning recovery post-surgically and also in acute and chronic heart failure[18]. This observation, also known as "the obesity paradox", states that an inverted J-shape curve exists between mortality and obesity (as shown in Graph 1.). This theory has recently been confirmed by a German study reporting an increased hospital mortality rate in underweight patients who were post-operatively admitted at the ICU compared with normal weight patients (17,8% versus 11.1%, $p=0.006$)[19]. Notably, in that study overweight and obesity were associated with a lower mortality rate ($p=0.047$)[19], but mortality increased in very obese patients (HR = 0.3, 95% CI = 1.06-8.48, P = 0.039)[19].
Several explanations for the obesity paradox (inversed J-shaped survival curve) have been proposed. The three most prominent are smoking as confounder, co-existence of an occult disease or so-called reverse causation[24], and the fact that BMI, its numerator being composed of both fat and fat-free mass, does not adequately represent the effect of fat mass on mortality rates[25].

In order to discriminate between muscle and fat mass induced weight several anthropometric parameters are used. For instance, intra-abdominal obesity, which is more prominent in obese patients, can be quantified by: WC, WHR and visceral adipose tissue (VAT). In a Mexican study in 88 patients, patients with android fat distribution and higher waist circumference are at greater risk for developing severe AP[26]. The same study group reported a stronger correlation between the umbilical WC and the development of SAP than parameters like BMI, minimum WC, waist-to-hip ratio and waist-to-thigh ratio[27]. More evidence pointing towards to the abdominal fat theory was provided by Yashima et al[28]. In their multi-variable analysis only volume of visceral adipose tissue (VAT) was strongly and negatively correlated to the course of an attack of acute pancreatitis. Other parameters, such as: BMI, subcutaneous adipose tissue, and WC (L2-L3 region), failed to reach statistical

significance. These findings are in line with our study, in which WC/BMI was significantly related to mortality in patients with predicted SAP.

Physiologic mechanisms for the protective effect of a higher BMI have been suggested, including the ability of adipose tissue to counteract higher levels of circulating inflammatory markers such as tumor necrosis factor, as well as increased nutritional and metabolic reserves[29-31]. In our study the multivariable analysis showed a significant inversed relation between BMI, mortality and morbidity, which could be related to the above mentioned theory. However, the individual complications (Table 2) and overall morbidity (multivariate) were significantly associated with an increased abdominal waist diameter (ventral-dorsal umbilical waist diameter, WC_{BMI}, WC/BMI), which suggests a negative effect of abdominal fat on overall morbidity.

Childers and colleagues propose an additional explanation[32]. They hypothesize that with obesity the mortality rates increase in the absence of major injuries or other diseases and mortality rates decrease in the presence of certain major injuries or other diseases. This hypothesis explains the inversed-J-shaped survival curve between BMI and mortality rates in our multivariable analysis [32] and the increased incidence of predicted severe acute pancreatitis in obese patients in the meta-analyses [13].

This study introduces the WC/BMI as a measure for central fatness. Separate multivariable analysis in which the WC was added to the BMI and rest of the parameters resulted in significant relations of both parameters with mortality (table 4). In other words: an increased WC/BMI results in additive and more powerful prediction of mortality than both parameters alone.

Definitions of Mortality, morbidity and ICU duration of stay were prospectively defined in this study cohort. Also the abdominal CT timing was prospectively defined and therefore, this study almost equals the quality of a prospective trial. A nationwide multicenter trial almost excludes local biases and represents a representative cross-section of the Dutch severe acute pancreatitis population.

There are several limitations of this study. First, the umbilical waist circumference was not measured on admission, but calculated using abdominal CT-scans by estimation of an elliptical shape. Second, from 32 patients the BMI was not retrievable from the case-record files (CRF. Third, smoking status, diabetes, and race were not noted in the CRFs and hence could not be accounted for. Finally, no information on the fat free mass and visceral adipose tissue (VAT) was available in this cohort.

In conclusion, this is the first study showing that the “obesity paradox” or an inverted (nadir) relationship between BMI and mortality rates exists in patients with a predicted severe acute pancreatitis. Furthermore, we confirm results from studies in patients with other criticall illnesses that also in predicted severe pancreatitis abdominal obesity is associated with an increased mortality and morbidity. This leads to the conclusion that obese patients suffering from a predicted severe attack of acute pancreatitis have a better outcome than non-obese patients, unless a patient has central obesity. Future (randomized) studies on acute pancreatitis should also stratify for (central) obesity, beside other well-known confounders.

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CHAPTER 9

SMOKING IS RELATED TO PANCREATIC FIBROSIS IN HUMANS

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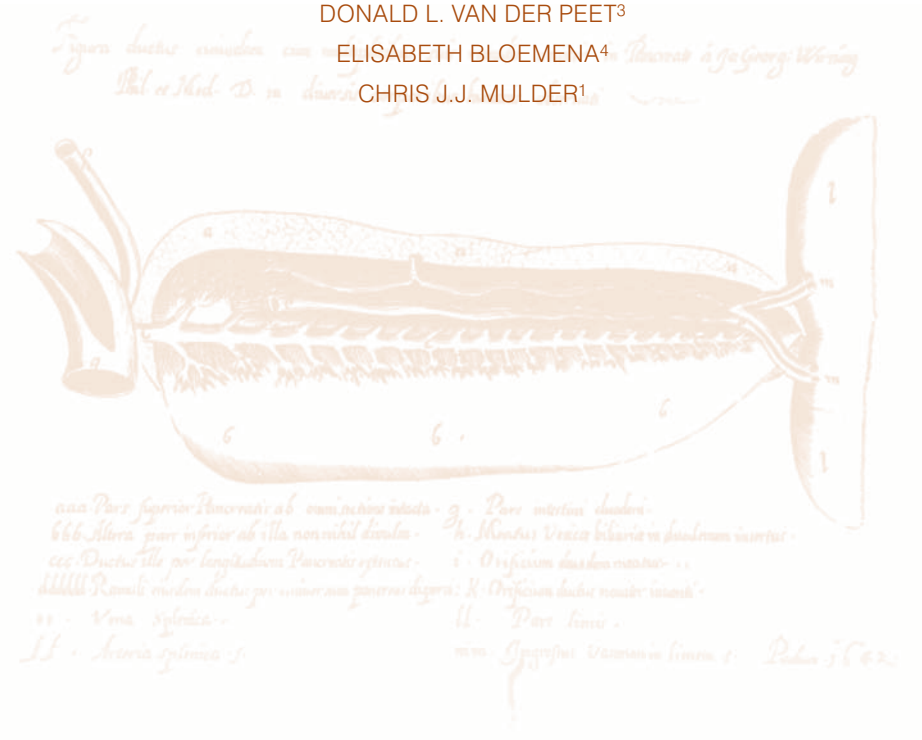

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ABSTRACT

Objectives: Smokers are at risk for pancreatic cancer (PC) and other pancreatic diseases. Cigarette smoking also aggravates the risk of PC in patients with hereditary and chronic pancreatitis (CP) and results in a higher incidence of acute pancreatitis and relapses in CP. Both PC and CP are characterized by a progressive fi brosis. Recently, two studies on rats reported that tobacco smoking is associated with chronic pancreatic inflammation with fibrosis and scarring of pancreatic acinar structures. In this study, we aimed to confirm a relationship between cigarette smoking and pancreatic fibrosis (PF) in humans.

Methods: In this retrospective study, pancreatic and liver tissue acquired during autopsy was collected and analyzed. PF was scored by assessing severity of intralobular, extralobular, and total PF: grade 0 (normal or mild; 0 – 25 % PF), grade 1 (moderate; 25 – 50 % PF), and grade 2 (severe; > 50 %). Information on smoking habits was extracted from (electronic) medical records.

Results: Of 900 autopsies performed from January 2005 to December 2007, a minority of patients ($n = 111$) met all inclusion criteria for analysis. Grade 2 – 3 total PF and intralobular PF was significantly more present in smokers vs. " never-smokers" (total: 42.9 vs. 26.5 % , $P = 0.027$ and intralobular: 39.3 vs. 15.6 % , $P = 0.013$), whereas no differences could be found between never-smokers and ex smokers and between ex-smokers and smokers. When we took into account interlobular PF, no differences between all groups were observed. No relationship between PF and age ($P = 0.893$), body mass index ($P = 0.707$), and pancreatic lipomatosis ($P = 0.916$) was observed.

Conclusions: To our knowledge, no study in humans had studied the effect of tobacco smoking on pancreatic tissue. We have demonstrated for the first time that current cigarette smoking is associated with total PF – specifically, intralobular PF – as compared with nonsmokers.

INTRODUCTION

Smoking tobacco exerts several eff ects in humans, including a pronounced carcinogenic effect on several organs. There is strong epidemiological evidence for a dose-dependent relationship between cigarette smoking and pancreatic cancer (PC). Cigarette smokers have a two- to threefold risk of developing PC compared with nonsmokers, and the risk remains higher for up to two decades aft er cessation of smoking (1 – 7). Pipe and cigar smokers have a lower risk of developing PC than cigarette smokers, with a relative risk between 0 and 2.1 (8,9). To date, no statistical relationship between passive smoking and the development of PC has been reported in the literature (4,10). Additionally, no relationship between smokeless tobacco and PC was observed in a recent meta-analysis (relative risk 1.03, 95 % confidence interval 0.71 – 1.49) (11).

Cigarette smoking is an independent risk factor in the development of and progression to chronic pancreatitis (CP) (12,13), and it results in a higher incidence of acute pancreatitis and relapses in CP (14 – 17). Smokers and patients with chronic and hereditary pancreatitis are at higher risk for PC (18,19). Furthermore, cigarette smoking increases the risk of the development of PC in patients with hereditary CP (15,20,21). The risk of smoking for the (progressive) development of PC and CP can be explained by the fact that CP is a precancerous condition.

Therefore, it can be assumed that tobacco smoking induces chronic pancreatic inflammation as a trigger for PC development.

Recently, more evidence for the theory that smoking induces chronic pancreatic inflammation was provided by two rat studies that investigated the effect of tobacco smoke inhalation on the pancreas. The investigators concluded that tobacco smoking is associated with chronic pancreatic inflammation with fibrosis, scarring of pancreatic acinar structures, and suppression of glutathione peroxidase activity (22,23).

To our knowledge, no previous study in humans had investigated the effect of smoking on pancreatic tissue. In this study, we aimed to confirm a relationship between cigarette smoking and pancreatic fibrosis (PF) and / or inflammation in humans.

METHODS

In this retrospective study, autopsy material consisting of pancreas and liver tissue from deceased patients at the VU University Medical Centre, Amsterdam, the Netherlands, was collected and analyzed. Patients 18 years and older were included (24). Exclusion criteria were as follows: (i) features consistent with hepatic or pancreatic disease as reported in medical records, (ii) a history of major abdominal

or gastrointestinal surgery (including small intestinal surgery or Billroth, Roux-en-Y anastomosis, Hepato-biliary, or pancreatic surgery because of possible hepatic / pancreatic lymphocytic infiltration), (iii) documented history of excessive alcohol intake (≥21 drinks / week for men and ≥14 drinks / week for women), (iv) severe postmortem changes that hampered histology, and (v) no documented smoking history.

Histopathology

Pancreatic tissue obtained during the autopsy was processed in a standard manner and stained with hematoxylin / eosin. All slides were evaluated under a light microscope (magnification ×100). The slides were assessed by an experienced hepatobiliary histo-pathologist (EB) and two research fellows (MS and EG), all blinded for patients ' clinical and laboratory data. Discrepancies were discussed.
PF was scored with the pancreas fi brotic score. Th is score emphasizes a subdivision between intralobular, extralobular and total PF: group 0 (normal or mild PF: < 25 % PF), group 1 (moderate PF: 25– 50% PF), and group 2 (severe PF: > 50%). Pancreatic lipomatosis was graded using the pancreatic lipomatosis score (PLS). This grading system emphasizes the distribution of intralobular, interlobular, and total pancreatic fat. The quantity of adipocytes per microscopic pancreas compartment (inter- and intralobular) was graded as follows: 0: 0 – 7 % adipocytes, 1: 8– 14%, 2: 15– 25%, 3: 26– 50%, and 4: > 51%. For the purpose of grading the total amount of fatty infiltration (inter and intralobular), a fifth group was added: > 75%. In addition, the presence of lymphocytes was noted.

Statistical analysis

To compare group characteristics, we used analysis of variance for continuous variables. Univariate ordinal logistic regression was used to test the relationship between ordinal histological parameters. Binary parameters were analyzed by binary logistic regression. Multivariate analysis (forward stepwise ordinal regression) was performed to correct for age, body mass index, and gender. A *P* value ≤0.05 was considered statistically significant. Results are presented as ordinal regression coefficients (B) and *P* values. All analyses were performed using SPSS soft ware version 17 for Windows (Chicago, IL).

Clinical data

Clinical and biochemical data were collected from electronic medical records and autopsy data. Anthropometric data comprised gender and body mass index. The medical data encompassed age, blood pressure, history of alcohol use, and smoking habits. Past history with respect to smoking; cardiovascular, liver, and gastroenterological diseases; and diabetes mellitus was noted. Smoking behavior

was noted as (i) " actual smoker, " a cigarette, cigar, or pipe smoker at the time of death; (ii) " ex-smoker, " quit smoking within the 10 years before death; and (iii) " never-smoker, " never smoked tobacco. Additionally, the cause of death was recorded.

RESULTS

Patient characteristics

More than 900 autopsies were performed in the VU University Medical Center from January 2005 to December 2007. During this period, 598 autopsies were performed on clinical patients of the VU University Medical Center. Of these patients, 415 met the inclusion criteria and were considered for this study. Of these, 259 subjects were excluded because of inferior quality of the histological material due to post-mortem changes ($n = 42$), absence of pancreatic and / or liver histological material ($n = 88$, cerebral autopsy only), known liver and / or pancreatic disease ($n = 41$ respectively $n = 28$), alcohol abuse ($n = 29$), or more than one reason ($n = 31$). Six patients were excluded because they had had major abdominal surgery: two Whipple operations, one Roux-Y-en anastomosis, one Billroth II, one hepatitis e. causa ignota (e.c.i.) after small intestinal surgery, and one right extended hemi-hepatectomy. Thirty-nine patients were excluded because no smoking history could be retrieved. Ultimately, 111 patients were eligible for analysis. Patient characteristics are shown in Table 1.

Table 1 Patient characteristics

	Never smoked (n=64)	Ex-smokers (n =19)	Actual smokers (n =28)	P value
Gender (men)	31 (48 %)	8 (42 %)	19 (68 %)	NS
Age ± s.d.	66.1± 15.9	67.4 ±9.2	64.6 ± 13.5	NS
BMI± s.d.	26.0 ± 4.5	28.5 ±6.2	24.5 ±5.0	NS
Case of death				
Cardiovascular	35 (55 %)	5 (26 %)	19 (68 %)	0.006
Gastrointestinal	1 (2 %)	1 (5 %)	1 (4 %)	NS
Malignancy	15 (23 %)	8 (43 %)	4 (14 %)	0.034
Other	12 (20 %)	5 (26 %)	4 (14 %)	NS

BMI, body mass index; NS, not significant. Ex-smokers: quit smoking within the past 10 years.

Smoking status, age, BMI, and pancreatic lipomatosis vs. PF

All the smokers and ex-smokers smoked cigarettes; none of the patients used smokeless tobacco. Because pack-years were not (accurately) noted in the medical records, no statistical calculations on this aspect could be performed.

The smoking status and PF grades are listed in Table 2 . For statistical analysis, PF was divided into two groups: group 1 (normal –mild PF) and group 2 (moderate – severe PF). Significantly more moderate – severe total PF was observed in the actual-smokers group vs. the never-smoked group (42.9 vs. 26.5 % , $P = 0.027$, Figure 1), whereas no significant difference in total PF was observed between the never-smokers vs. ex-smokers and ex-smokers vs. actual smokers ($P = 0.47$ and 0.32, respectively). Focusing on intralobular PF, the differences between the different smoking statuses were more pronounced (Figure 2): smoking vs. never-smoker (39.3 vs. 15.6 % , $P = 0.013$), ex-smoker vs. never-smoker ($P = 0.122$), and smoker vs. ex-smoker ($P = 0.589$). In the light of interlobular fibrosis, no statistical differences were observed between smokers vs. never-smoker, ex-smoker vs. neversmoker, and smoker vs. ex-smoker ($P = 0.754$, 1.00, and 1.00, respectively). No relationship between PF and age ($P = 0.893$), body mass index ($P = 0.707$), and total pancreatic lipomatosis ($P = 0.916$) was observed. The intralobular pancreatic lipomatosis was significantly inversely correlated with the total PF ($P = 0.034$). The inverse relationship between intralobular lipomatosis and intralobular fibrosis was even more pronounced ($P = 0.014$). Interestingly, no pancreatic inflammatory infiltrates were identified.

Table 2 Smoking status vs. pancreatic Fibrosis

	Never Smoked (*n* =64)	Ex-Smokers (*n* =19)	Actual Smokers (*n* =28)
Intrafibrosis Normal	54 (84 %)	13 (68 %)	17 (60.7 %)
Moderate	8 (12.5 %)	4 (21.1 %)	8 (28.6 %)
Severe	2 (3.1 %)	2 (10.5 %)	3 (10.7 %)
Interfibrosis Normal	55 (85.9 %)	16 (84.2 %)	23 (82.1 %)
Moderate	7 (10.9 %)	3 (15.8 %)	4 (14.3 %)
Severe	2 (3.1 %)	0 (0 %)	1 (3.6 %)
Total fibrosis Normal	47 (73.4 %)	12 (63.2 %)	16 (57 %)
Moderate	15 (23.4 %)	6 (31.6 %)	10 (35.7 %)
Severe	2 (3.1 %)	1 (5.3 %)	2 (7.1 %)

Ex-smokers: quit smoking within the past 10 years

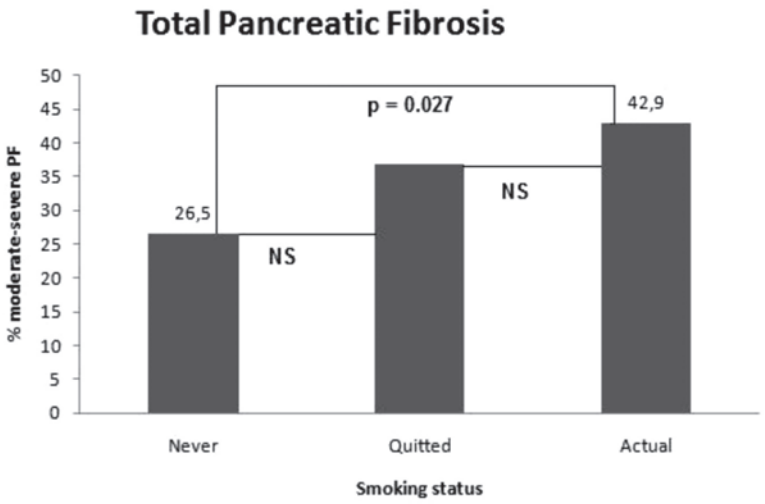

Figure 1 Smoking status vs. total pancreatic fibrosis (PF)

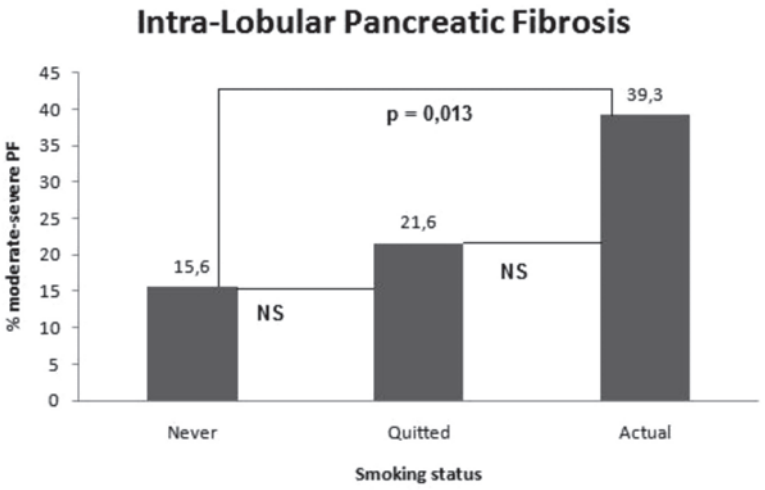

Figure 2 Smoking status vs. intralobular pancreatic fibrosis (PF)

DISCUSSION

To our knowledge, this is the fi rst study on PF in humans in relation to their smoking status. Overall, cigarette smokers had a significantly increased incidence of total PF compared with non smokers, consistent with the fi ndings of two animal studies. The first study that reported a relationship between pancreatic inflammation / fibrosis and smoking was performed in rats. The animals were exposed to either a high or low dose of environmental tobacco smoke twice a day for 12 weeks, after which an increase in pancreatic extracellular matrix among a decreasing number of acinar structures and infiltrating cells was detected (23). The second study, also in rats, reported inflammatory cell infiltration and ductal hyperplasia in pancreata after 12 weeks of exposure to cigarette smoke (22).
The relationship between smoking and the development of PF is a major element in CP, PC (25 – 27), postoperative pancreatic anastomotic leakage (28,29), and pancreatic exocrine insufficiency after a Whipple procedure (29,30). Two observational studies reported a significant relationship between cigarette smoking and pancreatic exocrine insufficiency (31,32). Cigarette smokers have significantly lower insulin levels and higher glucose levels compared with nonsmokers (31); PF could be a causative factor in this observation. Kim *et al.* (33) provided some evidence for this theory by reporting a relationship between activated pancreatic stellate cells (PSCs) and progression of islet fibrosis in type 2 diabetes.

Limitations of the study

This study has several limitations inherent to retrospective review of medical records, such as incomplete documentation (e.g., missing charts or unrecoverable or unrecorded information), difficulty in interpreting information found in the documents (e.g., owing to use of jargon and acronyms or unclear photocopies or microfiche), problematic verification of information and difficulty in establishing cause and effect, and variance in the quality of information recorded by medical professionals. Therefore, this study is more susceptible to documentation bias, selection bias, and potential confounders. One of the major limitations of this study was the lack of accurate information on smoking behavior of the deceased patients. Basic data regarding the number of pack-years and daily consumption of cigarettes were not noted in the autopsy reports or patient charts. Most Dutch citizens start to smoke between the ages of 14 and 25 years, with an average starting age of 15; the lifelong average of cigarette use is 15 cigarettes per day (source: Statistics Netherlands, http://www.CBS.nl , 18 December 2010). Considering the average age in our groups (~ 65 years), the estimated number of pack-years was more than 30 in our smokers group. The ex-smoker count in our study was low, which resulted in underpowered analysis concerning PF in this group.

No detailed information on duration of medication use was noted in our autopsy reports and patient records. Profound use of several drugs might act on PSCs. Potential fibrosis inhibitors have been reported in animal studies, including AT1 antagonists (angiotensin-converting enzyme inhibitors) (34,35), AT2 agonists (AT1 inhibitors, by not blocking AT2) (35), statins (36), and cyclooxygenase-2 inhibitors (37). In rat models, the nonsteroidal anti-inflammatory drug naproxen induced PF (38). Interestingly, Rothenbacher *et al.* (32) observed a decreased incidence of pancreatic exocrine insufficiency in patients taking angiotensin-converting enzyme inhibitors, possibly due to antifibrotic effects of angiotensin-converting enzyme inhibitors on the pancreas. These studies suggest that drugs can infl uence the PSCs. However, considering the fact that evidence on this subject is derived mainly on laboratory and animal studies, the possible consequences of these drugs on human PF are not known.

With regard to histology, there are three major limitations to the present study: (i) no information about the samples ' location in the pancreas, (ii) estimated quantification of PF, (iii) no additional PF staining, and (iv) no information about postmortem sampling time. The exact sample location was not known in our study. We assumed that the distribution of PF is uniform, but the actual PF pattern with respect to location in the pancreas is not known. However, in a study in rats, Wittel *et al.* (23) reported that cigarette smoke – induced pancreatic lesions were distributed throughout the entire gland without a greater prevalence in one specific area.

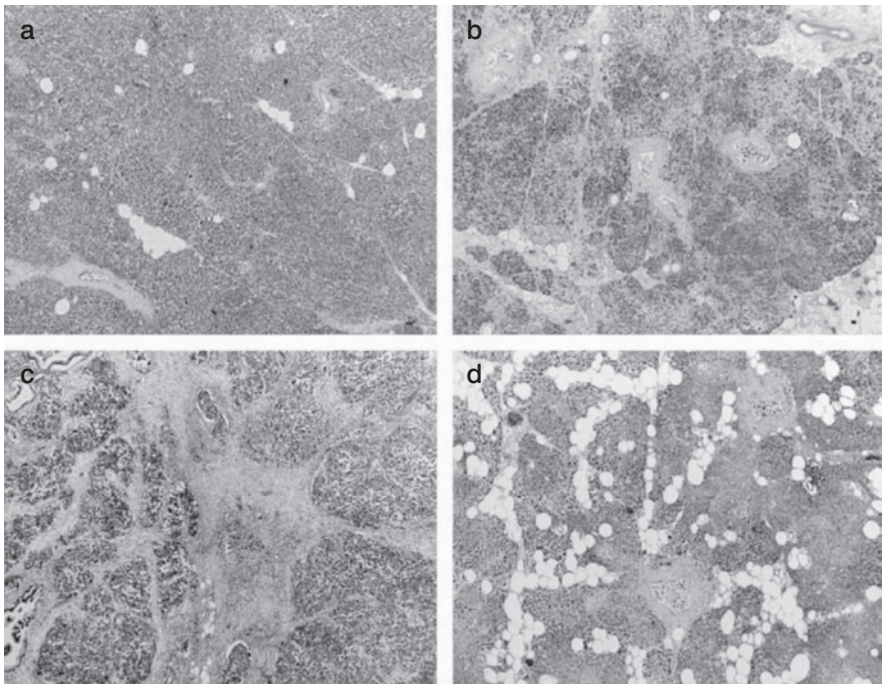

Figure 3 Hematoxylin and eosin – stained histology of the pancreas with respect to pancreatic fi brosis and lipomatosis

(**a**) normal histology, (**b**) interlobular fibrosis, (**c**) intralobular fibrosis, and (**d**) pancreatic lipomatosis.

The scoring of the pancreas fibrosis was performed via estimation, which is subjective. However, many pathological scores that are based on estimation of quantity (for instance, the non-alcoholic-steatohepatitis (NASH) score (24) and other PF scoring studies (30) are used in scientific papers and clinical practice. This study used hematoxylin/eosin staining for the quantification of PF. Fibrosis could easily be detected and quantified by estimation (see **Figure 3**). Because all slices were quantified in this manner, the (in)accuracy of estimating the amount of PF was consistent.

To date, no paper has reported the optimal postmortem sampling time for the pancreas. Only one letter to an editor suggested that the optimal sampling time is within 7 h (39). However, we do not know whether the scoring of fibrosis is negatively influenced by the sampling time, nor do we know the effect of the presence of fibrosis on the quality of the sample. Therefore, we think this is an interesting question that needs further investigation. To minimize this postmortem sampling time bias, we excluded all pancreatic samples for which there were signs of autolysis of the ductal epithelium, which resulted in exclusion of 42 specimens.

Hypothesis

The key player in PF is the PSC. PSCs, which are located in the interacinar spaces, account for ~ 4 % of all pancreatic cells in the healthy pancreas (26). PSCs exhibit limited proliferation and are characterized by the presence of vitamin A – containing fat droplets and absence of αsmooth muscle actin expression (26,40– 42). PSCs are activated by both internal stimuli (cytokines and growth factors produced by tumor cells, inflammatory cells, or injured resident cells) and external stimuli (oxidative stress, hyper glycemia, and alcohol) (26,40– 44). Aft er stimulation, PSCs phenotypically transform into myofibroblast-like cells that proliferate at high rate, lose the retinoid-containing fat-droplet synthesis ability, and produce large amounts of extracellular matrix proteins (mainly collagen type 1, laminin, and fibronectin) (41,42). Activated PSCs are capable of migration and phagocytosis (26), and they stimulate PC cell growth, angiogenesis, and desmoplastic reaction of PC (40,45). Hypothetically, oxidative stress induced by cigarette smoke and tobacco components could result in activation of the PSCs, which eventually results in PF, as our study suggests. Interestingly, in this study, the amount of intralobular, but not inter lobular, PF correlated significantly with cigarette smoking, which could be explained partly by the periacinar anatomical position of the PSCs.

In conclusion, cigarette smoking induces PF (mainly intralobular) in humans. This study provides additional evidence for the theory that smoking induces chronic pancreatic inflammation. Given that PF is associated with nearly all benign and malignant pancreatic diseases, smoking behavior should be accounted for in all studies and clinical practice when pancreatic disease is a potential confounder, and patients with pancreatic diseases should be encouraged to quit smoking.

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GENERAL DISCUSSION

GENERAL DISCUSSION

This thesis addresses studies concerning acute and chronic inflammation of the pancreas. The first part of the thesis contains studies regarding the diagnosis, treatment and incidence of acute biliary pancreatitis and azathioprine induced acute pancreatitis. The second part concerns the influence of obesity and smoking on the clinical course of pancreatitis and morphological aspects on the pancreas.

Part 1 Biliary and drug induced pancreatitis

In (**chapter 1**) an update is given concerning the etiology and diagnosis of acute biliary pancreatitis. Establishing a biliary etiology in acute pancreatitis is clinically important because of the potential need for invasive treatment, such as endoscopic retrograde cholangiopancreatography (ERCP) or a subsequent laparoscopic cholecystectomy. The etiology of acute biliary pancreatitis (ABP) is multifactorial and complex. A diagnosis of a biliary etiology in acute pancreatitis is supported by both laboratory and imaging investigations. An increased serum level of alanine aminotransferase (>1.0 μkat/l) is associated with a high probability of gallstone pancreatitis (positive predictive value 80–90%). Confirmation of choledocholithiasis is most accurately obtained using endoscopic ultrasonography or magnetic resonance cholangiopancreatography.

In (**chapter 2**) an evaluation of the treatment of acute biliary pancreatitis is given. A systematic review of previous meta-analyses and guidelines on ERCP in ABP was performed. There is consensus in both the meta-analyses and guidelines that ERCP is indicated in case of ABP with coexistent cholangitis and/or persistent cholestasis. By exception of the first meta-analysis, all included studies agreed that there is no place for early ERCP in predicted mild ABP. Consensus is lacking regarding the role of early ERCP in predicted severe ABP as 3 of the 8 meta-analysis and 1 of the 11 guidelines do not advice this strategy. Routine early ERCP in predicted severe ABP is recommend in 6 of the 11 guidelines. Indication of an endoscopic sphincterotomy is not well defined in meta-analyses and guidelines.

In the light of the somewhat confusing and in part conflicting recommendations found in (**chapter 2**) we investigated the opinion and attitude of Dutch gastroenterologists toward the application of (early) ERCP in the clinical management of ABP by means of a nationwide survey (**chapter 3**). In this survey, the vast majority of Dutch gastroenterologists attest to a role for ERCP in ABP, but indications when to perform ERCP, its timing, and the application of ES vary greatly and are not always in line with the Dutch or other published national guidelines. The results of this survey highlight the need for additional comparative randomized studies to define the role of (early) ERCP in ABP.

(**Chapter 4**) addresses the different treatment options for preventing recurrent attacks of acute biliary pancreatitis (RABP) including conservative treatment, cholecystectomy, ES, and combinations of these options. From the observational literature data it can be concluded that ES is as effective in reducing RABP as cholecystectomy but inferior in reducing mortality and overall morbidity. The combination of ES and cholecystectomy seems superior to either of the treatment methods alone. A prospective randomized clinical trial comparing ES plus cholecystectomy with cholecystectomy alone is needed.
In (**chapter 5**) the cumulative incidence and patient characteristics of thiopurine-induced acute pancreatitis in IBD patients is evaluated. Several reports suggest an increased rate of adverse reactions to azathioprine in patients with Crohn's disease. The cumulative incidence of thiopurine-induced acute pancreatitis in Crohn's disease equaled that of ulcerative colitis (UC) (2.6% vs. 3.7%) and this did not differ from vasculitis patients (2.6% vs.1.9%). In the IBD group, 100% of thiopurine-induced acute pancreatitis patients were women, whereas in the vasculitis group the two observed thiopurine induced acute pancreatitis cases (n = 2 of 2) concerned were men (P = 0.012). In this study, the alleged higher cumulative incidence of thiopurine induced acute pancreatitis in Crohn's disease compared with vasculitis or UC patients was not confirmed.

Part 2 Clinico-morfological studies on pancreatic lipomatosis and pancreatic inflammation

Obesity and insulin resistance cause fatty infiltration of many organs, including the pancreas (pancreatic steatosis [PS]) and the liver (nonalcoholic fatty liver disease [NAFLD]). In **(chapter 6)** we observed a relation between interlobular and total pancreatic fat with the NAFLD activity score, in patients without steatogenic medication. When corrected for body mass index (BMI), no relation could be found. Total pancreatic fat was a significant predictor for the presence of NAFLD but not for NASH. Presence of intralobular pancreatic fat was related to nonalcoholic steatohepatitis (NASH). This chapter demonstrates a relationship between NAFLD and PS, and, intralobular pancreatic fat and NASH. This relationships seem to be mediated by general obesity. The clinical significance of pancreatic steatosis is reviewed in (**chapter 7**). Multiple definitions, clinical associations and synonyms for pancreatic steatosis are described in the literature and can be confusing. In the past, pancreatic steatosis was considered an innocuous condition, a bystander of many underlying diseases (such as congenital syndromes, hemochromatosis and viral infection). However, evidence that pancreatic steatosis (strongly associated with obesity and the metabolic syndrome) has a role in type 2 diabetes mellitus, pancreatic exocrine dysfunction,

acute pancreatitis, pancreatic cancer and the formation of pancreatic fistula after pancreatic surgery is emerging.

In (**chapter 8**) the relation between (central) obesity and predicted severe acute pancreatitis is studied. Via a post-hoc analysis of a observational, multicenter study we included patients with a primary episode of predicted severe acute pancreatitis from a larger cohort of patients enrolled in a previous randomized clinical trial. Multivariable analysis showed an association between mortality and high waist circumference (WC)/BMI (OR 10.0, 95% C.I. 1.89-52.7), and a lower BMI (OR 0.84, 95% C.I. 0.71-0.99). For morbidity, multivariable analysis showed an association with a higher WC/BMI (OR 11.5 95% C.I. 2.07-63.8) and CTSI (OR 9.81, 95% C.I.: 3.22-29.2) and a lower BMI (OR 0.79, 95% C.I.: 0.66-0,94). With regard to ICU duration of stay, univariable analysis revealed an association between the CTSI ($p<0.0001$), ventral-dorsal umbilical waist diameter ($p<0.0001$) and the WC corrected for BMI ($p=0.003$). This is the first study to show that the "obesity paradox" also exists in patients with predicted severe pancreatitis. Mortality in obese patients with predicted severe pancreatitis is only higher as compared to non-obese patients when they suffer from central overweight. Whereas mortality in obese patients without central overweight is lower.

In **chapter 9** we investigate the effect of tobacco smoking on pancreatic inflammation and fibrosis. Smokers are at risk for pancreatic cancer (PC) and other pancreatic diseases. Cigarette smoking also aggravates the risk of PC in patients with hereditary and chronic pancreatitis (CP) and results in a higher incidence of acute pancreatitis and relapses in CP. Both PC and CP are characterized by a progressive fibrosis. In this retrospective study, we aimed to confirm a relationship between cigarette smoking and pancreatic fibrosis (PF) in humans, via pancreatic tissue acquired during autopsy. PF was scored by assessing severity of intralobular, extralobular, and total PF: grade 0 (normal or mild; 0-25% PF), grade 1 (moderate; 25-50% PF), and grade 2 (severe; >50%). Grade 2-3 total PF and intralobular PF was significantly more present in smokers vs. "never-smokers" (total: 42.9 vs. 26.5%, $P=0.027$ and intralobular: 39.3 vs. 15.6%, $P=0.013$), whereas no differences could be found between never-smokers and ex-smokers and between ex-smokers and smokers.

FUTURE PERSPECTIVES

Acute bilairy pancreatitis and drug induced pancreatitis

The role of an early ERCP in the treatment of predicted severe acute biliary pancreatitis will be investigated in the new APEC-trial (Acute Bilary Pancreatitis; early ERC/ES versus conservative treatment), that will start in the end of 2012. This trial will be coordinated by the Dutch Pancreatitis Study Group. In the RABP-study

(a follow-up study of the APEC: Recurrent Acute Biliary Pancreatitis Study) the rates of recurrent acute bilairy pancreatitis and other bilairy events will be studied in the cholecystectomy versus cholecystectomy /ES versus ES group (patients unfit for surgery). The outcome of this study will bring about the need of an updated biliary pancreatitis guideline. (New) Guideline adherence can be tested in the future via an questionnaire.

The literature on drug induced pancreatitis is scarce. Thiopurine induced pancreatitis seems to be an idiosyncratic reaction. However, after an e-mail correspondence with Professor Sachar (Mount Sanai Medical Center, New York), a dose dependent relationship seems to exist. He described a young male patient with Crohn disease (CD), who developed thiopurine induced pancreatitis after increasing the dosage of 6-MP. Re-challenge resulted in the same clinical picture. Additionally, in my IBD-praxis, I observed a similar case (young male, CD, acute pancreatitis after dose increase of 6-MP). Further investigation, in terms of genetic susceptibility, interval between drug initiation and development of pancreatitis and the presence or absence of thiopurine induced pancreatitis in 6-TG users will give us a more detailed picture of this disease.

Clinico-morfological studies on pancreatic lipomatosis and pancreatic inflammation

Pancreatic steatosis is a relatively new clinical entity. Little is known about its pancreatic distribution. A radiological and pathological study would give an insight in this topic or further studies. Normal value's of pancreatic steatosis and its relation to other syndromes and diseases are barley known. Case finding studies would be very welcome to define the quantity of steatosis in relation to certain diseases. The role of abdominal fat in relation to survival and morbidity in acute pancreatitis is getting clearer. However, more research in terms of fat-distribution, nutritional status, smoking behavior in relation to morbidity and mortality in acute pancreatitis is need. The role of smoking and pancreatic diseases is clearly underlined in the last years. However, exact mechanism of inflammation, fibrosis (pancreatic stellate cel activation) genetic susceptibility and its clinical consequences, such as: pancreatic insufficiency, operative outcome (after Whipple: peri-operative and long term morbidity and mortality), are unknown.

ADDENDUM

NEDERLANDSE SAMENVATTING
LIST OF PUBLICATONS
DANKWOORD
CURRICULUM VITAE

NEDERLANDSE SAMENVATTING

INLEIDING

Een aanval van een acute alvleesklierontsteking (acute pancreatitis) komt in de wereld voor met een aantal van 5-80 per 100.000 inwoners per jaar (jaarlijkse incidentie). In Nederland is deze jaarlijkse incidentie 19 per 100.000 inwoners per jaar. Tussen de 3 en 10.7 procent van de patiënten met een aanval van een acute pancreatitis sterft er tussen de 3 en 10.7%. Helaas blijft het sterfte percentage de laatste 4 decennia stabiel. De twee meest voorkomende ooraken van acute pancreatitis (70-80% van alle oorzaken)zijn galwegstenen en alcohol. Andere oorzaken zijn: buiktrauma, ischemie, chirurgie, ERCP, pancreaskanker, anatomische varianten van het galwegsysteem/pancreas, autommuun ziekten, hyperlipidemie, drugs, geneesmiddelen, infecties, genetisch en idiopathisch. Het geslacht is sterk geassocieerd met het risico op een aanval van acute pancreatitis. Mannen krijgen vaker een alcoholische pancreatitis en vrouwen vaker een galsteen (of biliaire) pancreatitis.

OPBOUW VAN HET PROEFSCHRIFT

Het proefschrift bestrijkt gebieden in de pancreatologie:

1. Klinische studies naar biliaire en geneesmiddel geïnduceerde acute pancreatitis
2. Clinico-morfologische studies naar pancreasvervetting en pancreasverbindweefseling/ontsteking.

Deel 1 Klinische studies naar biliaire en geneesmiddel geinduceerde acute pancreatitis

Hoofdstuk 1

Het vaststellen van een biliaire etiologie in acute biliaire pancreatitis (ABP) is van klinisch belang, omdat ere en potentiele behandeling kan plaats vinden met een ERCP. De etiologie van een ABP is multifactorieel en complex. De passage van kleine galblaassteentjes of sludge (zandachtig gruis), door de uitgang van de galwegen naar de 12-vingerige darm lijkt belangrijk voor de pathogenese. Andere factoren lijken ook hun steentje bij te dragen, zoals: anatomische varianten (inductie van biliopancreatische reflux), gal en pancreassap exclusie van de 12-vingerige darm (duodenum), en genetische factoren. De diagnose van een ABP wordt ondersteund door laboratoriumwaarden en beeldvorming. Een verhoogd serum ALT van meer dan 1μkat/l is geassocieerd met een hoge kans op een biliaire vorm

van pancreatitis (positieve predictieve waarde van 80-90%). De bevestiging van galwegstenen wordt het meest accuraat gedaan met een endo-echo of MRCP.

Hoofstuk 2

Verschillende gerandomiseerd studies hebben de rol van een ERC en endoscopische sphincterotomie (ES) bestudeerd in ABP. In dit hoofdstuk worden de uitkomsten van verschillende meta-analysen en richtlijnen naast elkaar gelegd om te bekijken of er een internationale conscensus is m.b.t .de behandeling van acute biliaire pancreatitis. Doormiddel van een systematische review (en de PRISMA-richtlijnen) wordt er een literatuur search gehouden. Uit deze review kwam naar voren dat er consensus was over de behandeling van patiënten met een ABP en cholangitis en blijvende cholestase, heirbij is een snelle ERCP/ES geïndiceerd. In vormen van voorspeld milde ABP wordt op 1 meta-analyse na, geadviseerd om de patiënt conservatief te behandelen. In het geval van een voorspeld ernstige ABP zijn de uitkomsten en aanbevelingen van meta-analysen en richtlijnen sterk verdeeld.

Hoofdstuk 3

In hoofdstuk 4 bestuderen we de opinie en attitude van de Nederlandse endoscopist/MDL-arts, aangaande de behandeling van ABP: vroege ERCP/ES versus een conservatieve aanpak. Via een enquête onder al de MDL-artsen (n=283, respons ratio van 52%) kwam naar voren dat 96.6% van de MDL-artsen een rol zag weggelegd voor een vroege ERCP bij de behandeling van ABP. Veertien procent van de ondervraagde gaf zelfs aan altijd een ERCP/ES te verrichten bij een ABP. De rest van de groep gaf aan, onder bepaalde voorwaarden een ERCP te verrichten, zoals: gedilateerde galweg (95%), galwegstenen (72%), cholangitis (87%), geelzucht (59%), ampullaire steen (68%), en bij een voorspeld ernstige ABP (35%). De helft van de ondervraagden vonden een ERCP binnen 24 uur na opname of klachten het beste tijdstip voor een ERCP. In 55% van de gevallen, waarbij er een ERCP wordt verricht, wordt er zo wie zo een ES verricht, zonder duidelijke reden. Deze enquête laat zien dat de overgrote meerderheid geloofd in een vroege ERCP/ES bij ABP. Echter, de timing, indicatie en applicatie van een ES zijn niet altijd in overeenkomst met de Nederlandse richtlijnen. Deze studie geeft aan dat er eendduidelijkere studies en richtlijnen op dit vlak gewenst zijn.

Hoofdstuk 4

Een hernieuwde aanval van een ABP (HABP) kan worden voorkomen dor een galblaasverwijdering (de bron van galsteen aanmaak). Sinds de introductie van de ERCP/ES, zijn er verschillende series die een gelijkwaardige preventie beschrijven m.b.t. het voorkomen van een HABP in vergelijking met een galblaasverwijdering.

In hoofdstuk 4 reviewen we de verschillende behandelingsopties aangaande de preventieve behandeling voor het tegengaan van een HABP, zoals een conservatieve therapie, galblaasverwijdering, ERCP/ES en combinaties van beide opties. De uitkomsten waren als volgt: een galblaasverwijdering en ERCP/ES waren superieur t.o.v een conservatieve behandeling in het voorkomen van HABP. Echter een galblaasverwijdering geeft ook bescherming tegen galsteen/blaas gerelateerde complicaties. Observationele studies laten zien dat een combinatie van een galblaasverwijdering en ERCP/ES een lagere aantal HABP geven dan een van de modaliteiten alleen. Het is noodzakelijk deze strategie uit te zoeken in een prospectieve gerandomiseerde studie.

Hoofdstuk 5

In hoofdstuk 5 onderzoeken we of de bewering van verschillende studies of de kans op een thiopurine geïnduceerde pancreatitis hoger is in patiënten met M. Crohn (CD) dan in patiënten met een colitis ulcerosa (CU) of vasculitis (VA). Door middel van een retrospectieve studie met data uit 3 ziekenhuizen (241 patienten met CD en CU, 108 patienten met VA). De cumulatieve incidentie van thiopurine-geinduceerde acute pancreatitis verschilde niet tussen de CD en UC groep (2.6% vs 3.7%). Ook de was de cumulatieve incidentie van patienten met CD of UC niet verschillend van de VA-patienten. Er bestond een duidelijke vrouwelijke predominantie bij de thiopurine geïnduceerde pancreatitis bij IBD patiënten. Terwijl in de VA groep er alleen maar mannen met een thiopurine geïnduceerde pancreatitis waren.

Deel 2 Clinico-morfologische studies naar pancreasvervetting en pancreasverbindweefseling/ ontsteking.

Hoofdstuk 6

Overgewicht en insuline resistentie zorgen voor een vettige infiltratie van meerdere organen, zoals: pancreas (pancreatische steatose-PS) en lever (nonalcoholic fatty liver disease-NAFLD). Doormiddel van een post-mortum studie op 80 patiënten worden de coupes van de lever en het pancreas bestudeerd op de vervettingsgraad. De interlobulaire en totale vervetting graad van het pancreas zjn gerelateerd aan de aanwezigheid van NAFLD. De intralobulaire vervettingsgraad was gerelateerd aan de aanwezigheid van non-alcoholic steato-hepatitis (NASH). Dit is de eerste studie in de literatuur, die een relatie tussen NASH en PS laat zien.

Hoofdstuk 7

De verschillende definities en associaties van/met klinische entiteiten en PS worden onderzocht in een pubMed search. Vroeger dacht men dat PS een “onschuldige voorbijganger” was. Echter, met de huidige associatie van PS met het metabool

syndroom, hemochromatose, virale infecties, exocriene pancreas insufficiëntie, acute pancreatitis, pancreas kanker en ontstaan van fistels na pancreas chirurgie, lijkt PS niet meer zo onschuldig.

Hoofdstuk 8

Zoals boven beschreven, lijkt het erop dat overgewicht leidt to een ernstiger verloop van een aanval et acute pancreatitis. Dit blijkt uit meerdere studies en meta-analysen. Echter, obese mensen hebben een hogere incidentie van acute pancreatitis, wat leidt tot een over-representatie van obese patiënten in een acute pancreatitis cohort. Verder is het percentage voorspeld ernstige acute pancreatitis hoger bij obese dan bij niet obese patiënten, hetgeen automatisch leidt tot een over- representatie van ziekere patiënten in de obesitas-groep, waardoor het lijkt dat het obees zijn gecorreleerd is aan een slechtere overleving bij patiënten met een acute pancreatitis. In studies met kritisch zieke patiënten komt juist naar voren dat obese mensen juist beter overleven dan magere of mensen met een normaal postuur. Worden ze ernstig obese kan neemt de sterfte kans weer toe. Dit fenomeen wordt de omgekeerde J-curve (overleving versus BMI) of Obesity-Paradox genoemd. In hoofdstuk 8 wordt via een post-hoc analyse van een observationele, multicenter studie, waarbij er alleen patiënten met een ernstige pancreatitis worden geincludeerd, gekeken of een hoog BMI en andere antropometrische waarden leiden tot een grotere morbiditeit en mortaliteit. Bij 144 patiënten met een voorspeld ernstige pancreatitis kwam uit de multivariabele analyse naar boven dat de sterfte kans toenam bij patiënten met een normaal of laag BMI en een hoge buikomvang gerelateerd aan de BMI (WC/ BMI, afgeleide van abdominaalvet). Uit deze studie kun je concluderen dat een hoog BMI leidt tot minder kans op sterfte bij obese patiënten met een voorspeld ernstige pancreatitis, tenzij de patiënten een centrale (abdominale) obesitas hebben.

Hoofdstuk 9

Rokers hebben meer risico op het krijgen van pancreas kanker, exocriene en endocriene pancreas insufficiëntie, chronische pancreatitis en acute pancreatitis. Zowel pancreas kanker als chronische pancreatitis hebben pancreas fibrose als gezamenlijke uiting van inflammatie. Twee ratten studies hebben een verband laten zien tussen pancreas fibrose/ inflammatie en roken. In hoofdstuk 9 bestuderen we het rookgedrag in relatie tot de pancreasfibrose d.m.v. een post-mortum studie.
De pancreasfibrose werd gescoord (kwantitatief d.m.v. schatting) in relatie tot het rookgedrag. In 111 patienten werd dit onderzoek verricht, waarbij het opviel dat matig-ernstige totale fibrose en intra-lobulaire fibrose vaker voorkwam bij rokers dan bij niet rokers (totaal: 42.9 vs. 26.5 % , $P = 0.027$ and intralobular: 39.3 vs. 15.6 % , $P = 0.013$). Dit is de eerste humane studie die een relatie tussen pancreas fibrose en het rookgedrag legt.

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CURRICULUM VITAE

Erwin-Jan Mathieu van Geenen werd geboren op 25 februari 1969 te Eindhoven. Na het behalen van het HAVO en VWO diploma in respectievelijk 1987 en 1989 (Rommert Cazimir College te Eindhoven en Maurick College te Vught), werd hij 5x uitgeloot voor geneeskunde en startte met de geneeskunde opleiding aan de Vrije Universiteit Brussel. Als lid van het Universitaire squash team nam hij deel aan de landelijke competitie. Tijdens zijn studie werkte hij als taxichauffeur, vakkenvuller (Valtax/ EDAH, Vught) en docent anatomie (UU) om de studie te bekostigen. In 1994 werd hij ingeloot voor geneeskunde en startte hij met de studie farmacie in Utrecht. Aan de Universiteit Utrecht behaalde hij zijn doctoraal farmacie/ geneeskunde en artsexamen in 1998,1999 en 2001. In verband met vrijstellingen (vanuit de VUB) kon er geen cum laude voor beide studies verleend worden. Tijdens de studies werd er onderzoek verricht bij de afdeling Biotechnologie (Prof Dr W. Hennink), MDL (Prof Dr M. Samsom) en algemene heelkunde (prof Dr Th.J.M.V. van Vroonhoven). Na het artsexamen werkte hij 1 jaar als arts-assistent chirurgie (Eemland Ziekenhuis, Prof Dr Th.J.M.V. van Vroonhoven). Daarna volgde de opleiding tot transplantatiechirurg aan de Universitätsklinikum Leipzig (Prof Dr J. Haus). De opleiding werd, op eigen verzoek en tegen advies in van de opleider en opleidingsteam gestaakt, omreden van: arbeidsomstandigheden, financiële onoverkomelijkheden en sociale druk. Hierop aanvaarde hij een functie bij Sanofi-Synthelabo (tegenwoordig Sanofi-Aventis), als Regional Healthcare Development Manager. Toen hij het aanbod kreeg om na 9 maanden manager van de afdeling te worden, kreeg hij de mogelijkheid om de langgewenste opleiding tot MDL-arts te volgen, bij Prof Dr Chris Mulder. De drie-jarige interne vooropleiding werd gevolgd in Zwolle aan de Isala Klinieken (Dr M. van Marwijk Kooy) en in Amsterdam aan de VU (Prof Dr B.A.C. Dijkmans). Vervolgens werd met de perifere MDL-stage aangevangen in juli-2006 in het MCA (Opleider H.A.R.E. Tuynman). In januari 2007 startte hij in het VUMC (Prof Dr Chris Mulder). 1-juli-2009 werd hij MDL-arts, (aandachtsgebied geavanceerde endoscopie). Na zijn opleiding werd hij maatschapslid van de afdeling MDL in het Bronovo ziekenhuis, verbracht hij 2 dagen per week in het l'Hôpital Erasme (Université Libre de Bruxelles, Prof Dr J. Deviere), en kreeg hij een nul aanstelling bij de afdeling MDL van het VUMC, voor endo-echo training (Dr M.A.J.M. Jacobs). Per 1-september 2012 is hij staflid van afdeling MDL van het Radboud UMCN. Erwin van Geenen woont samen met zijn partner Antoinette Tolkamp en zijn 2 kinderen: Quinten en Xavier. Naast zijn passie voor techniek in de geneeskunde, is er een adoratie voor Duitsland en (snelle) automobielen. Het koppel is met enige regelmaat op de Bundesstraße en Autobahn te vinden, al dan niet vergezeld van zijn gezin. Freude am Fahren!