Chronic pancreatitis & pancreatic cancer

the Clinical Aspects and Treatment of Pancreatic Exocrine Insufficiency

Edmée C.M. Sikkens

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You only live once,
but if you do it right,
once is enough

– Mae West –

Voor mijn ouders en zusjes

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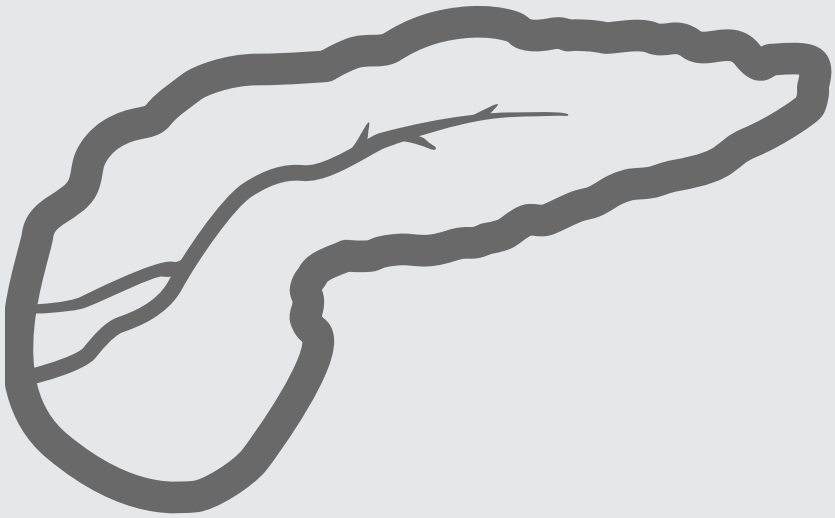
Chapter 1 *Introduction and outline of the thesis*



INTRODUCTION

In exocrine pancreatic insufficiency, the pancreas is unable to deliver a sufficient quantity of pancreatic enzymes to the small intestine to digest food. It may occur in several life threatening diseases, including chronic pancreatitis and pancreatic cancer. Due to this lack or absence of pancreatic enzymes, malabsorption of fat develops, which causes steatorrhea-related symptoms, weight loss, and malnutrition. To reduce morbidity and even mortality, patients should be treated with a sufficient amount of oral pancreatic enzymes.

In clinical practice, enzyme supplementation therapy seems to be a challenge, because the optimal enzyme dose is highly variable, depending on the remaining pancreatic function, the postsurgical anatomy, and dietary fat content. Unfortunately, this seems to be an underexposed topic (as the literature overview in chapter 2 shows), and physicians are often not well informed about the need to supplement exocrine insufficiency in a patient-tailored manner. In addition, exocrine insufficiency is frequently overlooked, because the primary attention is directed towards treatment of the underlying disease. Despite the seriousness of this condition, so far, both research and guidelines have given very little attention to the importance of diagnosing and optimizing treatment efficacy of exocrine pancreatic insufficiency.

AIM

The general aim of this thesis was to explore various clinical aspects of exocrine pancreatic insufficiency in chronic pancreatitis and pancreatic cancer. First, an attempt was made to gain insight in the current practice of enzyme supplementation, in particular the prevalence of under-treatment and its consequences. Furthermore, possible strategies to improve treatment outcome were researched.

OUTLINE OF THESIS

In **chapter 2**, we give an overview on the current status on how exocrine pancreatic insufficiency should be diagnosed and treated. Because data regarding the practice of pancreatic enzyme replacement therapy are lacking, we prospectively evaluated if patients with exocrine insufficiency caused by chronic pancreatitis are properly treated. The results of this evaluation are described in **chapter 3**. In **chapter 4**, we also evaluated this in patients after pancreatic surgery. Their results were compared with exocrine insufficient patients who had not been operated upon.

Because exocrine insufficiency leads to malabsorption, patients are at risk to acquire deficiencies of the fat-soluble vitamins (vitamin A, E, D, and K). It may even result in a decreased bone mass and the development of osteopenia and osteoporosis. Because few studies have addressed this topic, we evaluated this in chronic pancreatitis patients according to exocrine function status and enzyme use in **chapter 5**.

In cancer of the pancreatic region, exocrine insufficiency may also develop. Because survival is improving due to novel treatment forms in these patients, diagnosing and treating exocrine insufficiency is getting more important. So far, the natural course of the exocrine function in pancreatic cancer is unknown and the risk of patients developing exocrine insufficiency is not well established. In **chapter 6**, we therefore prospectively assessed this function on a monthly base from time of diagnosis in inoperable patients to preclude the confounding effects of pancreatic resection. In **chapter 7**, we evaluated the effect of resective surgery on the exocrine function in pancreatic cancer patients from diagnosis until 6 months after surgery.

Although the optimal enzyme dose is highly variable, in clinical practice, most patients use a fixed number of capsules. In **chapter 8** we challenged the effect of extensive patient education regarding flexible self-dosing on treatment outcome.

Finally, in **chapter 9**, we summarize and discuss the main findings of the studies presented in this thesis. In addition, we present potential clinical implications and suggestions for future research.

Chapter 2 *Pancreatic enzyme replacement therapy in chronic pancreatitis*

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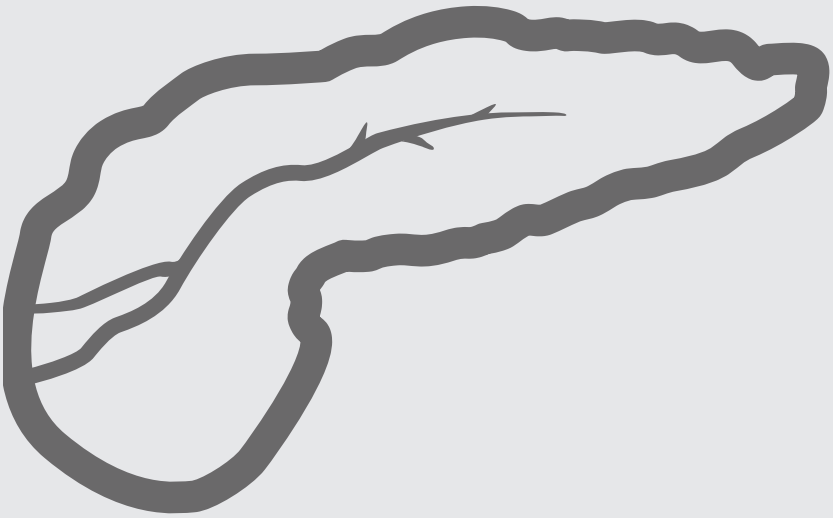

ABSTRACT

Exocrine pancreatic insufficiency (EPI) is a serious condition, which occurs in several diseases including chronic pancreatitis (CP), cystic fibrosis, pancreatic cancer, and as a result of pancreatic surgery. The lack or absence of pancreatic enzymes leads to an inadequate absorption of fat, proteins, and carbohydrates causing steatorrhea and creatorrhea, which results in abdominal discomfort, weight loss and nutritional deficiencies. To avoid malnutrition related morbidity and mortality, it is pivotal to commence pancreatic enzyme replacement therapy (PERT) as soon as EPI is diagnosed. Factors as early acidic inactivation of ingested enzymes, under dosage, and patient incompliance may prevent normalization of nutrient absorption, in particular of fat digestion. This review focuses on the current status of how to diagnose and treat EPI.

Keywords: chronic pancreatitis, exocrine pancreatic insufficiency, pancreatic enzyme replacement therapy

EXOCRINE PANCREATIC INSUFFICIENCY AND CHRONIC PANCREATITIS

In EPI, the pancreas is unable to deliver sufficient amounts of pancreatic enzymes to the small intestine to digest intraluminal nutrients. EPI may occur due to loss of functional parenchyma (atrophy), blockage of the pancreatic duct, or postprandial asynchrony. Besides CP, other conditions that can result in loss of parenchyma are severe acute pancreatitis (which can cause transient EPI), pancreatic resection, and cystic fibrosis (CF). Chronic obstruction of the main pancreatic duct can be caused by strictures, ductal stones in CP, or due to a malignancy. Postprandial asynchrony is the disjunction between gastric emptying of a meal and the delivery of pancreatic enzymes into the small intestine, which can occur as a result of gastric resection, gastric bypass surgery, short bowel syndrome, Crohn's disease and diabetes mellitus[1, 2]. In CP, the progression to gland failure depends on the underlying cause of the disease[3]. Patients with alcoholic pancreatitis for instance, develop exocrine insufficiency after a median time period of ten years while in patients with idiopathic CP this may take up to 20 to 25 years to occur[4]. Furthermore, in autoimmune pancreatitis, EPI is one of the presenting symptoms in over 75% of patients[5, 6].

PANCREATIC SECRETION

The pancreas plays a crucial role in the digestive system. The gland produces pancreatic juice that consists of a mixture of more than two-dozen digestive enzymes in the pre-activated form, called zymogens. Zymogens are produced by acinar cells and mixed with a bicarbonate rich fluid that is produced by pancreatic ducts cells[2, 7]. Trypsinogen is the most important zymogen because it becomes trypsin, the key enzyme that activates all other zymogens. Trypsin, chymotrypsin, amylase and lipase are responsible for the majority of the enzyme activity derived from the pancreas[7]. Lipase is one of the most important enzymes, because it plays a leading role in the digestion of fat, which is the highest dietary source of calories. There are three types of lipase: lingual, gastric, and pancreatic. Approximately 10-30% of the lipolytic activity can be attributed to gastric and lingual lipase[8, 9]. This explains the residual fat digestion and absorption in pancreatectomized individuals. After exocrine pancreatic enzymes are secreted in the duodenum, they move to the ileum and during this intestinal transit the intraluminal activity of the enzymes diminishes due to irreversible proteolytic and acidic degradation. There is a considerable variability in the intraluminal stability of the different pancreatic enzymes[10, 11]. Lipase is the most susceptible to acidic and proteolytic degeneration and is therefore available for a shorter period during small intestinal transit in patients with EPI as well as in healthy people[11-13]. In healthy people, 74% of the amylase activity, 22% of the trypsin activity and just 1% of the lipase activity survive intestinal transit[11]. The digestion and absorption of lipids takes place between the pylorus and the ligament of Treitz[14]. Digestion in the jejunum and the ileum is less efficient. In meals with a high concentration of fat the physiologic malabsorption of several grams of fat occurs. A fecal fat excretion of up to 7 g/d can therefore be considered normal.

PATHOPHYSIOLOGY

The pancreas has a large functional reserve and clinically evident EPI occurs only when 90% of the function is lost and the secretion of pancreatic enzymes is less than 10% of normal[15, 16]. Because of a decrease in lipase, trypsin and amylase activity, maldigestion of fat, proteins and carbohydrates occurs. Malabsorption of fat precedes malabsorption of proteins and carbohydrates and is clinically more apparent[11, 17, 18]. The decrease in pancreatic lipolytic activity cannot be compensated effectively by other mechanisms. As a consequence, the increased presence of lipids and other nutrients in the distal small bowel causes significant alterations in gut motility leading to accelerated gastric emptying and intestinal transit. This results in a marked decrease in the time available for digestion and absorption of nutrients, which contributes to the malabsorption[14, 16, 19-21]. Furthermore, in diabetic patients, autonomic neuropathy may further accelerate the early arrival of chyme to the cecum as well[22]. There is one additional factor that may contribute to impaired lipolysis. In EPI the secretion of bicarbonate by the pancreas is considerably diminished. Normally, bicarbonate protects pancreatic enzymes from denaturation by gastric acid. Due to the low bicarbonate secretion, the intraduodenal pH may drop below 4 late postprandially, which negatively affects lipase activity[23]. Another effect of the diminished bicarbonate secretion is that bile salts may precipitate, which leads to a decrease in postprandial duodenal lipid solubilisation[24].

SYMPTOMS AND COMPLICATIONS

In CP patients with EPI, maldigestion of dietary macronutrients (fat, proteins and carbohydrates) leads to malnutrition, which is associated with various health problems. Maldigestion of fat results in steatorrhea, which causes symptoms such as foul smelling, voluminous, greyish, fatty stools, abdominal cramps, bloating, and chronic abdominal pain[25]. In addition, steatorrhea may cause weight loss due to the loss of the highest dietary source of calories (fat contains 38 kJ/g, carbohydrates and protein contain 17 kJ/g)[26-28]. Maldigestion secondary to CP is associated with deficiencies of fat-soluble vitamins (vitamin A, D, E, and K), magnesium, calcium, and essential fatty- and amino acids[29-31]. Deficiencies in these vitamins and nutrients may lead to tetany, glossitis, cheilosis, and in a more progressive stage, to peripheral neuropathy[32]. In addition, patients with EPI are at risk of developing significant bone loss. Because these patients have decreased serum levels of vitamin D metabolites and a low bone mass, it seems reasonable to consider a bone density scan to check for signs of osteoporosis[33, 34]. Several studies have reported malabsorption of zinc in advanced CP, but the mechanism of this phenomenon remains unclear[35, 36]. Folate deficiencies, although rare, have been reported because folate forms insoluble complexes with pancreatic extracts[37, 38]. Furthermore, reduced plasma levels of high-density lipoprotein C, Apo A-I and lipoprotein A, which are protective factors

against atherogenesis, have been observed in CP patients[39], which may explain the increase in cardiovascular events in EPI. In one study cardiovascular risk factors were investigated in 54 CP patients. In 33%, clinical and laboratory evidence of arterial involvement was found. In 15% of the CP patients electrocardiographic alterations indicating coronary heart disease were observed and 22% had peripheral symptoms and signs indicating atherosclerotic disease of the lower extremities[40]. Another study demonstrated that in a group of 57 CP patients approximately 61% presented with aortic calcifications in comparison with 30% of the healthy controls[41]. Several studies have reported an increased morbidity and mortality in CP patients with EPI[40, 41] and therefore, early detection and effective treatment of EPI is of clinical importance.

DIAGNOSIS

The pancreatic exocrine function can be tested in an invasive or a non-invasive manner. With invasive testing, which is considered to be the golden standard, pancreatic enzymes are measured in pancreatic juice that is collected from the duodenum after intubation (intraduodenal lipase output after intravenous administration of 1 U/kg CCK; normal value, >90 kU/hr)[42]. Pancreatic enzyme stimulation in these tests can be either direct, by means of the intravenous administration of hormones like secretin, or indirect, by using a test meal (Lund test meal). Because of the invasive nature this test is reserved for research purposes and in clinical practise, non-invasive testing is preferred.

The non-invasive technique is based on the measurement of products of digestion that are either passed in the stool or absorbed and detected in breath[2, 43]. Many non-invasive pancreatic function tests are available, but the perfect test does not exist. The ideal test should be easy to perform, inexpensive, and precise; with an adequate sensitivity and specificity not only in patients with severe CP, but also in mild to moderate disease without signs of steatorrhea.

Although maldigestion of fat is one of the main symptoms of EPI, the measurement of faecal fat is not an accurate test. Nevertheless, the faecal fat collection test is often used to quantify steatorrhea although it suffers from many drawbacks. First, it is not a specific test for EPI, because steatorrhea may be caused by other conditions such as celiac disease, Crohn's disease or bacterial overgrowth. Second, it is not a very sensitive test, because as noted earlier, steatorrhea due to pancreatic maldigestion occurs only when more than 90% of the pancreatic function is lost. Third, the patient must discontinue PERT for about a week prior to the test. Finally, measuring the faecal fat excretion is cumbersome because it requires a 72-hour collection of stool after a standardized fixed diet of 80 – 100 g of fat/day. Qualitative measurement of a single stool specimen is useless, because fat content varies with the dietary fat intake[44]. There is, however, a relatively new test to evaluate fat malabsorption that does not require stool collections

or discontinuation of PERT. The ^{13}C-MTG breath test consists of the oral administration of ^{13}C-marked substrates with a test meal. The proportion of substrates that are hydrolyzed in the intestinal lumen are absorbed and finally released across the pulmonary endothelium as $^{13}CO^2$, which is measured in a breath sample. The ^{13}C-MTG breath test has a sensitivity of 89% and specificity of 81%[42]. Its greatest use may be to detect steatorrhea in mild to moderate disease and to assess the efficacy of PERT[45-47]. At present, the faecal elastase-1 test (FET) is the most popular test to evaluate EPI[48]. The FET measures the production of human elastase-1 in stool (normal value >200 µg/g)[49]. The test is easy to perform; requiring a single stool sample only, which can be stored at room temperature for up to five days, and PERT may be continued[50]. The sensitivity is approximately 100% in severe EPI, but the test is less reliable in mild to moderate disease with a sensitivity of 77 – 100% to detect moderate EPI and 0 – 63% to detect mild EPI[48, 51]. It has a specificity of approximately 93%[52], but can be compromised in patients with small bowel disease and type 1 Diabetes. There is also the chance of a false-positive outcome in patients with diarrhoea and other intestinal disorders[49].

The faecal chymotrypsin test (FchT) is a less reliable test to evaluate EPI, but may be used to evaluate treatment efficacy and compliance[53, 54]. Chymotrypsin evades degradation in stool by binding to insoluble debris and is stable for several days at room temperature[55]. The chymotrypsin activity is measured from spot stool samples with a cut of value of <3 U/g[56]. The FchT is altered by exogenous enzymes and is therefore useful to monitor for compliance[55]. The test has a sensitivity ranging from 50 – 80% for advanced EPI[57], but only 50% for mild to moderate EPI[58]. Also, the specificity is lower than the FET[57]. Chymotrypsin can be variably affected during intestinal transport and may be diluted in the presence of concomitant diarrhoea. Another disadvantage of this test is that patients have to stop PERT two days prior to the stool collection[56]. Finally, in clinical practise, another commonly used way to diagnose EPI is to establish significant improvement in maldigestion-related symptoms with a trial of PERT[2].

TREATMENT

The treatment of EPI in CP consists of the oral administration of a combination of pancreatic enzymes during meals[59]. Every patient with EPI and maldigestion, independent of the degree of steatorrhea and presence or absence of associated symptoms, should receive PERT[60, 61]. The main focus in the management of EPI is to prevent weight loss, EPI related symptoms, vitamin deficiencies, and to improve the nutritional status[25, 62]. The most important clinical parameter to monitor treatment efficacy is body weight. Several studies have demonstrated that in most patients one year of PERT resulted in significant weight gain[46]. However, abnormally low nutritional parameters have been demonstrated in approximately 70% of CP patients despite adequate clinical control with PERT[47]. Therefore, vitamins and nutrients should also be monitored.

PANCREATIC ENZYME REPLACEMENT THERAPY

The exogenous pancreatic enzymes currently used, are primarily extracted from porcine sources. These enzyme preparations, also called pancrelipase or pancreatin, contain a variable mixture of protease, lipase and amylase depending on the brand. Various pancreatin preparations are available consisting of capsules containing mini-microspheres, pellets or microtablets of less than 2 millimetres in size. They are designed to promote an adequate intragastric mixture of exogenous enzymes with chyme[63-67]. These pH-sensitive microspheres are coated with polymers that are acid resistant and release the enzymes above a safe pH threshold (pH 5.0–5.5) to avoid acid denaturation of pancreatic enzymes in the stomach[66, 68]. Several pancreatic enzyme formulations available on the European market were evaluated *in vitro* and were all shown to contain the lipase dosage they claimed[69]. There are however differences in galenic properties and release kinetics[66]. An *in vitro* study evaluating nine different pancreatic enzyme products using the current United States Pharmacopeia (USP) methodology showed that enzyme contents were comparable, but the percentage of lipase activity after dissolution varied[70]. Although formal *in vivo* evidence is lacking these differences could influence efficacy, at least from a theoretical standpoint, and therefore it is not uncommon in clinical practice to substitute one PERT for another in case of incomplete treatment response[66, 70-72]. In vivo studies in patients with chronic pancreatitis did not show delayed emptying of larger (2 mm) spheres and release of enzymes in relation to a meal[63].

DIET AND DOSAGE RECOMMENDATIONS

Despite the absence of an easy applicable and objective method to establish the adequate dose of oral pancreatic enzymes in EPI, some general guidelines can be given to accomplish a patient tailored administration schedule[73]. In the past, the restriction of fat was the only way to reduce steatorrhea, but with the introduction of PERT, this is no longer advocated. Instead, the dose of PERT is tailored to the fat intake of the patient. In general, the recommended dosage of PERT for a main meal (breakfast, lunch, or dinner) ranges from 25,000 – 75,000 units of lipase and from 10,000 – 25,000 units of lipase for snacks, depending on the fat content of the meal. At present, there are two preparations available: a high dose ('HL') preparation, containing approximately 25,000 units of lipase and a low dose ('LD'), which contains 6,000 – 10,000 units of lipase. The timing of ingestion of the capsules is important to optimize therapeutic efficacy. Half of the dose should be swallowed at the start of the meal and the remainder should be taken halfway the meal[2, 4, 23, 74, 75]. This improves the intragastric mixture of the enzymes with the chyme and therefore simultaneous gastric emptying into the duodenum[23, 74].

Besides PERT, the management of EPI consists of dietary counselling to improve digestion[60]. A dietician is able to give dietary advice and explain proper enzyme use according to fat intake. The highest relieve of symptoms is reached by self-dosing of pancreatic enzymes according to fat intake, compared with a fixed-dose regimen. A study proved that this resulted in a significant increase of the number capsules a day from 5 to 11.5, accompanied with a decrease of bowel movements and abdominal pain[76]. Dietary counselling is also important, because many patients avoid different nutrients (e.g. fats, carbohydrates and proteins) to prevent steatorrhea related complaints.

WHEN TREATMENT FAILS

In case of treatment failure, several causes should be considered. A common cause for treatment failure is under dosing of pancreatic enzymes. The practical and reasonable first step therefore is to increase the dose of pancreatic enzymes guided by fat resorption and clinical response, up to a maximum of 10,000 IU lipase/kg/day. This latter recommendation stems from treating children with cystic fibrosis. Evidently, in adult patients with exocrine insufficiency such high dosages are not reached. The majority of adult patients are adequately treated with 6 to 12 capsules containing 25,000 units of lipase per day. Second, the patient might be incompliant or may not use enzymes properly due to miscomprehension. Evidently, patient education by the treating physician and dietician should solve this problem.

If the treatment response remains unsatisfactory, inhibition of gastric secretion can be attempted by administration of a proton pump inhibitor. If the patient still not responds, other diseases such as celiac disease and bacterial overgrowth, which may also cause maldigestion and steatorrhea, should be ruled out[76-79]. A last resort may be the restriction of fat. This should be imposed under supervision of a dietician. When necessary, a loss in caloric intake can be compensated by an energy-enriched diet. When feasible, both meal density and frequency should be increased (≥6)[80].

TOXICITY AND SIDE EFFECTS

Very few side effects have been observed when using PERT. High doses of enzymes can induce transient nausea, bloating, diarrhoea and hypersensitivity. Only one serious adverse event has been reported. In January 1994, Smyth et al. described five children with CF in which a colonic obstruction developed due to fibrosing colonopathy (FC) after using very high doses of the enteric-coated micro-minisphere preparations[81, 82]. The mechanism underlying this phenomenon remains unclear. Although cases of FC have been described in CF without the exposure to

pancreatic enzymes, it seems that the development of FC is undoubtedly provoked by the use of pancreatic enzyme preparations. Fortunately, the cases of FC have decreased considerably since the MCA recommended that the dose of pancreatic enzymes should not exceed 10,000 IU lipase/kg/day in patients with CF in 1994[83].

CURRENT RESEARCH AND EMERGING ALTERNATIVES

Bovine enzymes

In patients who refuse to consume porcine products for religious or other cultural reasons, bovine enzymes appear to be an attractive alternative[84]. However, bovine preparations contain about 75% less lipase activity compared to porcine and human pancreatic extracts. Hence, a considerable greater amount of tablets needs to be taken to treat EPI in comparison with porcine preparations. Furthermore, there are some concerns about transmittable pathogens which can cause diseases as foot-and-mouth disease and Bovine spongiform encephalopathy[85]. These disadvantages have prohibited bovine pancreatic enzymes to become a commercial alternative for porcine enzymes.

Fungal derived lipase

An alternative could also be fungal derived lipase, which has the advantage that it is acid resistant. Unfortunately, studies have demonstrated that there are some disadvantages. First, fungal lipase gets rapidly inactivated in the presence of low concentrations of bile salts. Furthermore, fungal lipases are swiftly eliminated by proteases[86]. Results of in vivo studies with fungal lipase demonstrated that they are much less effective than porcine pancreatic extracts[86-88].

Bacterial lipase

The use of bacterial lipase seems more promising, because it shows a significant lipolytic activity. Bacterial lipase is stable against proteolytic hydrolysis and is not inactivated by bile salts[89], resulting in a much higher lipolytic activity than the conventional porcine preparations[90, 91]. Several studies suggest that the efficacy of bacterial lipase is directly related to the fat content of the diet;[90] with an absorption of about 70% in a low-fat diet and 90% in a high-fat diet[92, 93].

A potential problem with bacterial lipase is that it only restores one pancreatic enzyme, and not proteases and amylase. It is unsure what the clinical (side) effects of such mono enzyme therapy will be. Because there is little experience with bacterial lipase in humans, further studies are needed to test safety and efficacy.

Human lipase

Another rather futuristic but intriguing development is the restoration of a patient's own bio-engineered lipase production with gene therapy. Human lipase genes have been successfully transfected and expressed using a recombinant adenovirus in a human gallbladder cell line in vitro, a sheep gallbladder ex vivo, and in the bile ducts of rats in vivo[94, 95]. Using the gallbladder as a target for gene therapy is an interesting option but many challenging issues need to be resolved[96]. First of all, the method to insert the gene in vivo must be further developed. Second, gene expression must be high enough to reach adequate levels of enzyme activity in the small bowel and persist for an adequate time period, to limit the need for repeat procedures. Therefore, this is a truly futuristic outlook for which much more work needs to be done before this technique is ever ready to be used in humans.

SUMMARY

Clinically evident EPI occurs when 90% or more of the pancreatic function is impaired and the secretion of pancreatic enzymes is less than 10% of normal. It is of great importance to actively look for EPI, recognize it as early as possible, and start PERT to avoid malnutrition related morbidity and mortality. The most readily available and easiest test for a clinician to detect EPI is the FET. Every patient with EPI and maldigestion, independent of the degree of steatorrhea and presence or absence of associated symptoms, should receive PERT. The main focus in the management of EPI is to prevent weight loss, EPI related symptoms (e.g. steatorrhea, abdominal cramps, etc.), vitamin deficiencies and to improve nutritional status. The most important clinical parameter for monitoring treatment efficacy is body weight. Therapy consists of patient tailored administration of enzymes in the form of enteric-coated mini-microspheres. In general, the recommended dosage of PES for a main meal (breakfast, lunch or dinner) ranges from one to three capsules (containing 25,000 units of lipase) and 1 capsule (containing 10,000 to 25,000 units of lipase) for snacks, depending on the fat content of the meal. The efficacy of enzymes seems to be higher when they are divided over the meal. When initial treatment fails, a proton pump inhibitor can be added after the dosage has been increased up to a maximum of 10,000 IU lipase/kg body weight per day. A normal fat intake should be encouraged within the limits of patient's own tolerance preferably under the guidance of a professional dietician.

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Chapter 3 *Patients with exocrine insufficiency due to chronic pancreatitis are undertreated; a Dutch national survey*

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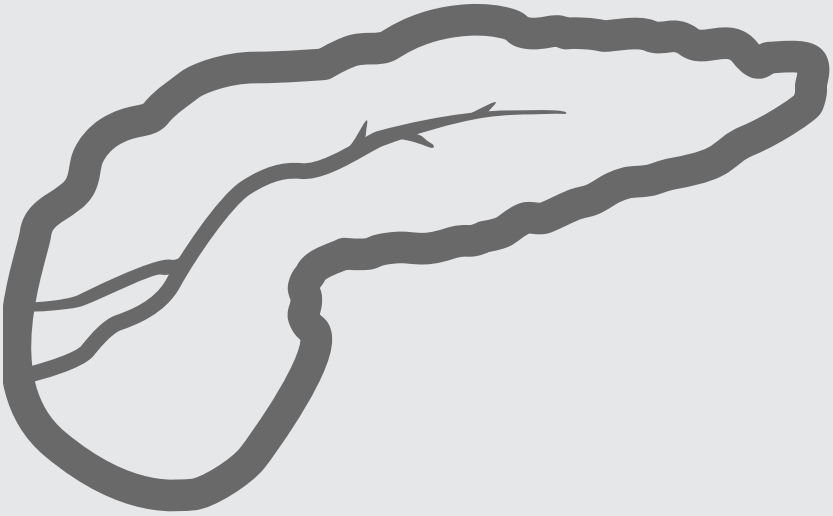

ABSTRACT

Introduction

Treating exocrine pancreatic insufficiency with pancreatic enzymes is challenging, because there is no fixed dose regimen. The required dose varies per patient, depending on the residual pancreatic function, the gut lumen physiology, and the fat content of each meal. Using a sufficient dose of enzymes is crucial to prevent weight loss, nutritional deficiencies, and to ameliorate steatorrhea-related symptoms. Data regarding the practise of enzyme replacement therapy are lacking. Therefore, we evaluated if patients with exocrine insufficiency caused by chronic pancreatitis receive proper treatment in the Netherlands.

Methods

An anonymous survey was distributed to the members of the Dutch Association of Patients with Pancreatic Disorders. The survey focused on enzyme use, steatorrhea-related symptoms, dietary consultation, and food restrictions. Responding patients were included if they had chronic pancreatitis and were treated for exocrine insufficiency with pancreatic enzymes.

Results

The survey was returned by 178 members, who suffered from chronic pancreatitis, 161 of whom (90%) met the inclusion criteria. The mean age was 56 years and 53% were male. The median enzyme intake was 6 capsules per day and 25% of patients took 3 or less capsules. Remarkably, 74% of patients still reported steatorrhea-related symptoms, despite treatment. Only 25% of cases were referred to a dietician and 58% kept a restriction of fat (either instructed by a dietician or self-imposed).

Conclusions

Many patients with exocrine insufficiency caused by chronic pancreatitis are under-treated in the Netherlands, a country with a well-organized healthcare system. To improve treatment efficacy, patients should be educated in adjusting the enzyme dosage according to steatorrhea-related symptoms and dietary fat intake. Moreover, patients should be referred to a well-trained, specialized dietician.

Keywords: chronic pancreatitis, exocrine pancreatic insufficiency, steatorrhea, weight loss, pancreatic enzyme replacement therapy

INTRODUCTION

In exocrine insufficiency the pancreas is unable to deliver sufficient amounts of digestive enzymes to the small intestine, leading to maldigestion[1-3]. Malabsorption of fat results in steatorrhea, which causes symptoms such as voluminous and greasy stools, abdominal cramps and bloating[4]. Malabsorption also leads to weight loss and malnutrition[5-7]. It is associated with deficiencies of fat-soluble vitamins, magnesium, calcium, and essential fatty and amino acids[8-10]. These deficiencies may cause tetany, glossitis, cheilosis, and in a more progressive stage, peripheral neuropathy[11]. Patients with exocrine insufficiency are also at risk of developing significant bone loss[12, 13].

Because of the increased morbidity, it is important that all patients with exocrine insufficiency receive proper treatment as soon as the diagnosis is made, independent of symptoms[14-17]. The goal is to ameliorate symptoms, to prevent weight loss, and to improve the nutritional status by prescribing a sufficient dose of pancreatic enzymes[4, 18]. The optimal enzyme dose is variable, depending on the remaining pancreatic function and the dietary fat content, which makes treatment complex. Data regarding the practise of enzyme replacement therapy are lacking. Therefore, we evaluated if patients with exocrine insufficiency caused by chronic pancreatitis receive proper treatment in the Netherlands.

METHODS

This prospective, cross-sectional study was approved by the Medical Ethics Committee of the Erasmus University Medical Center. An anonymous survey was distributed by mail among members of the Dutch Association of Patients with Pancreatic Disorders, a patient organization for pancreatic diseases. After 4 weeks, a reminder was sent out to members that had not responded. The survey contained free field and multiple-choice questions and took about 10 minutes to complete (appendix 1). The questions focused on enzyme use, the presence of steatorrhea-related symptoms (abdominal cramps; bloating; voluminous, sticky, and greasy stools), referral to a dietician, and food restrictions.

Patients were eligible for this study if they had chronic pancreatitis and were using pancreatic enzymes to treat exocrine insufficiency. There were no exclusion criteria. The primary endpoint was the daily enzyme dose, recalculated as the number of capsules containing 25,000 FIP-E units of lipase. Secondary endpoints were: the presence of steatorrhea-related symptoms, referral to a dietician, and a restriction of fat (recommended by a dietician or self-imposed).

Statistical analyses were conducted using SPSS 17.0. Results were expressed as medians and percentiles, using the appropriate t-tests or non-parametric tests for continuous variables. For categorical data, the X^2 test was used.

RESULTS

Hundred-and-seventy-eight members suffering from chronic pancreatitis responded to this survey, of which 161 (90%) were using enzyme replacement therapy for exocrine insufficiency. The mean age of this study population was 56 (±12) years and 53% were male. Hundred-and-fifteen patients (71%) were being treated by a specialist (gastroenterologist, internist, or surgeon) and 46 (29%) were followed by their general practitioner.

Patients were prescribed a median of 4 capsules a day when treatment was commenced. At the time of completing this survey, the median treatment duration was 77 months. The median enzyme dose had increased to 6 capsules per day. However, 25% of cases used 3 or less capsules per day (Table 1). Furthermore, 74% of the patients reported steatorrhea-related complaints, despite treatment, and 49% suffered from weight loss.

Table 1. Starting dose and current dose (at time of completing the survey) of pancreatic enzymes of 161 patients with chronic pancreatitis

	Patients	**Starting dose**	**Current dose**	***p*-value**
	25%	≤ 3	≤ 3	
Enzyme dose/day*	50%	≤ 4	≤ 6	< 0.01
	75%	≤ 6	≤ 8	

* Number of enteric coated capsules containing 25,000 FIP-E units of lipase

Only 40 cases (25%) reported to have visited a dietician for their exocrine insufficiency. Remarkably, dietary consultation did not affect treatment efficacy. As summarized in Table 2, the enzyme dosage, restriction of fat, weight loss, and steatorrhea-related complaints did not improve. Nevertheless, patients who where referred to a dietician were significantly more satisfied with the information they received regarding enzyme use (p-value <0.005).

Table 2. Treatment outcome of enzyme replacement therapy in 161 patients with chronic pancreatitis, according to referral to a dietician

	Total population	**Dietician +**	**Dietician -**	***p*-value**
Patients per group – no. (%)	161 (100)	40 (25)	121 (75)	
Current enzyme dose/day* – median	6	6	5	
Steatorrhea-related complaints – no. (%)	119 (74)	37 (78)	82 (68)	NS
Weight loss – no. (%)	79 (49)	14 (35)	65 (54)	NS
Fat restriction – no. (%)	93 (58)	23 (58)	70 (58)	NS

* Enteric coated capsules containing 25,000 FIP-E units of lipase

DISCUSSION

Exocrine insufficiency is a common complication of chronic pancreatitis, but also of pancreatic cancer and pancreatic surgery. This study shows that a considerable proportion of patients with exocrine insufficiency due to chronic pancreatitis are under-treated. Despite enzyme replacement therapy, most patients were still bothered by steatorrhea-related symptoms. Furthermore, a dietician was seldom consulted, and if so, this did not improve treatment outcome.

This poor outcome may be explained by the complexity of enzyme replacement therapy. The enzyme dose needs to be individually adjusted, based on the residual pancreatic function, the gut lumen physiology, steatorrhea-related complaints, and dietary fat intake[19-26]. Because the optimal dose is so variable, there are no official guidelines for physicians to consult. Also, publications on this subject are scarce, and therefore, physicians are not well informed about the intricacies of treating exocrine insufficiency. Furthermore, exocrine insufficiency is not only undertreated, but probably also under-diagnosed[27]. Unfortunately, assessment of the pancreatic function is not seldom forgotten, as attention is focused on treating the primary disease.

Few studies have evaluated the efficacy of pancreatic enzyme suppletion in chronic pancreatitis. One randomised trial has compared the efficacy of a fixed enzyme dosage to self-administration ad libitum[28]. Ramo et al. treated patients for 4 weeks according to each regimen. There was a significant increase from 5 (+/- 1.3) capsules per day during the fixed treatment period to 11.4 (+/- 2.4) capsules per day during the self-administration period (p-value <0.001). Furthermore, a significant decrease in steatorrhea-related symptoms was seen. Therefore, they concluded that self-administration is more efficient.

We recommend that, to achieve optimal treatment efficacy, patients should be instructed to vary the dose according to their dietary fat intake, up to a maximum of 16 capsules a day. In addition, it should be explained that the presence of steatorrhea-related symptoms and weight loss imply an insufficient dose of enzymes that needs to be increased. Also, it would

be beneficial to refer patients to a well-trained, specialized dietician, to educate them about the principles of treatment and prevent them from keeping unnecessary dietary restrictions, because many patients tend to avoid fat out of fear for steatorrhea-related complaints.

Our study was bound to certain limitations. First of all, due to the anonymous character of the survey (which was required by the medical ethical committee), certain information about the patient population was unavailable. Therefore, we were unable to calculate the response rate, to provide information about the lifestyle of patients, and the aetiology and severity of the pancreatitis. Furthermore, there is some subjectivity in the data that were collected. For example, the presence of steatorrhea-related symptoms could not be verified. In addition, other factors might have influenced the outcome measure of weight loss, such as pain, incompliance, and co-morbidity. A selection bias could have occurred because this survey was distributed amongst members of a patient organization, who are generally highly motivated and better informed. Therefore, this study may have overestimated the efficacy of treatment.

This study is the first to capture how patients with exocrine insufficiency are actually being treated, and gives an insight in the clinical treatment efficacy. The results imply that, even in a well-organized country as the Netherlands, a considerable proportion of patients are underdosed and therefore, treatment needs to be improved. For one, physicians should be better educated in dosing pancreatic enzymes in a flexible manner and a practice guideline is desperately needed. Also, well-trained, specialized dieticians should be involved, to help educate patients.

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Appendix 1: Patient survey; questions regarding enzyme replacement therapy, symptoms and referral to a dietician

Question 1
How many pancreatic enzyme-replacing capsules are you **currently** using per day?

.....

Question 2
What kind of capsules do you use *(check all applicable boxes)*

Creon ☐
Creon "Forte" ☐
Panzytrat "LD" ☐
Panzytrat "HL" ☐
Pancrease ☐
Other, namely .....

Question 3
How many pancreatic enzyme capsules did you use per day in the past, at the time when treatment was commenced?

.....

Question 4
Do you keep dietary restrictions, and if so, what kind?

.....

Question 5
Do you **currently** have symptoms of:

Fatty diarrhea *(frequent, voluminous stools that stick to the toilet bowl)*	yes / no
Stomach cramps and/or bloating	yes / no
Weight loss	yes / no

Question 6

Has a dietician ever been involved,	yes / no
when pancreatic enzyme-replacement therapy was prescribed	

Question 7

If yes, did you find the co-treatment by a dietician useful	yes / no

Chapter 4 *The daily practice of pancreatic enzyme replacement therapy after pancreatic surgery, a northern European survey*

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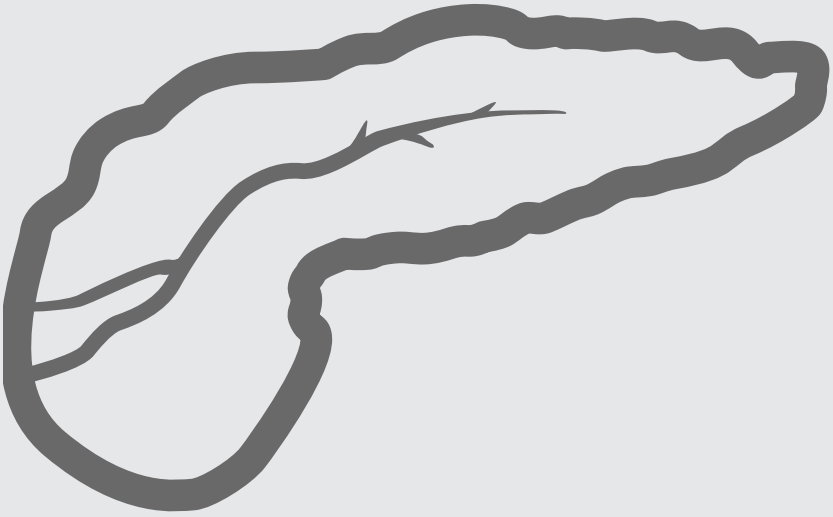

ABSTRACT

Introduction

After pancreatic surgery, up to 80% of patients will develop exocrine insufficiency. For enzyme supplementation to be effective, prescribing an adequate dose of pancreatic enzymes is mandatory but challenging, because the required dose varies. Data on the practice of enzyme replacement therapy after surgery are lacking and therefore we conducted this analysis.

Methods

An anonymous survey was distributed to members of the Dutch and German patient associations for pancreatic disorders. The target population consisted of patients with chronic pancreatitis or pancreatic cancer who had undergone pancreatic surgery and were using enzymes to treat exocrine insufficiency. Results were compared to a similar group of non-operated patients.

Results

Ninety-one cases were analyzed (84% underwent a resection procedure). The median daily enzyme dose was 6 and 25% took 3 or less capsules. Despite treatment, 68% of patients reported steatorrhea-related symptoms; 48% adhered to a non-indicated dietary fat restriction; and only 33% had visited a dietician. The outcome was equally poor for the 91 non-operated patients.

Conclusions

Most patients suffering from exocrine insufficiency after pancreatic surgery are under-treated. To improve efficacy, physicians should be more focused on treating exocrine insufficiency and educate patients to adjust the dose according to symptoms and their diet.

Keywords: chronic pancreatitis, pancreatic cancer, exocrine pancreatic insufficiency, pancreatic surgery, pancreatic enzyme replacement

INTRODUCTION

In exocrine insufficiency the pancreas is unable to deliver sufficient quantities of digestive enzymes to the small intestine. Because of the large residual capacity of the pancreas, exocrine insufficiency becomes clinically apparent only when 90% of the function is lost[1, 2]. After pancreatic surgery, the exocrine function is determined by the underlying pancreatic disease and the chosen surgical procedure (depending on the extent of the resection and the restoration of gastrointestinal tract continuity)[3, 4]. Postoperatively, exocrine insufficiency is observed in 65 to 80% of the patients with chronic pancreatitis[5, 6]. In patients with pancreatic cancer, exocrine insufficiency is found in 68% to 92% before surgery and in 80% after surgery[7].

Exocrine insufficiency leads to malabsorption, which causes steatorrhea, weight loss, and malnutrition[8-11]. It is associated with deficiencies of the fat-soluble vitamins (vitamin A, D, E, and K), magnesium, calcium, and essential fatty and amino acids[12-15]. To reduce morbidity and mortality, patients should be treated with a sufficient dose of pancreatic enzymes[16-19]. In clinical practice, enzyme replacement therapy proves challenging, because the optimal enzyme dose is highly variable, depending on the remaining pancreatic function, the postsurgical anatomy, and the dietary fat content. Unfortunately, physicians are often not well informed about the need to supplement exocrine insufficiency in a flexible and patient tailored manner. In addition, exocrine insufficiency is frequently overlooked, because the primary attention is directed towards treatment of the underlying disease. This may be especially true for surgeons who are confronted with a patient with pancreatic cancer, because their main concern is to explore curative options.

Remarkably, data on the clinical practice of enzyme replacement therapy in surgically treated patients are lacking. Therefore, this survey was conducted to evaluate the daily practice of enzyme replacement therapy in postoperative patients.

METHODS

This prospective, cross-sectional study was approved by the Medical Ethics Committee of the Erasmus University Medical Center in Rotterdam. In 2010, an anonymous survey was distributed among the members of the Dutch and German patient associations for pancreatic disorders. The target population consisted of surgically treated patients with chronic pancreatitis or pancreatic cancer who were using enzymes to treat exocrine insufficiency. We also assessed the responding members who fulfilled the criteria of the target population, but had not been operated upon.

The survey was distributed by mail and had to be returned within 3 months. After 4 weeks, a reminder was sent out to the members that had not responded. The survey contained free field and multiple-choice questions and took about ten minutes to complete. The items evaluated in the survey were the daily enzyme dose (recalculated as the number of capsules containing 25,000 FIP-E units of lipase), the timing of enzyme ingestion, the presence of steatorrhea-related symptoms (bloating; abdominal cramps; bulky, sticky, and fatty stools), referral to a dietician, and restrictions in fat intake (either recommended by a physician or dietician, or self-imposed).

Statistical analyses were conducted using SPSS 17.0. Results were expressed as medians and percentiles, using the appropriate t-tests or non-parametric tests for continuous variables. For categorical data, the X^2 test was used.

RESULTS

Two-hundred-and-sixty-five members responded to the survey, of which 182 (69%) had chronic pancreatitis or pancreatic cancer and were using pancreatic enzymes for exocrine insufficiency. The baseline characteristics of these 182 patients are described in Table 1. Ninety-one of these patients had undergone pancreatic surgery (84% underwent a resection procedure and 16% a drainage procedure; Table 2). The remaining 91 patients had not been operated upon.

Table 1. Baseline characteristics of 182 operated and non-operated patients with exocrine insufficiency caused by chronic pancreatitis and pancreatic cancer

	Operated patients N = 91	**Non-operated patients** N = 91
Age – median (IQR)	60 (49 – 68)	57 (50 – 67)
Male sex – no. (%)	44 (48)	41 (45)
Chronic pancreatitis – no. (%)	54 (59)	83 (91)
Pancreatic cancer – no. (%)	37 (41)	8 (9)
Supplementation duration – median mo (IQR)	54 (28 – 131)	60 (49 – 68)

The enzyme preparations used by the study population were all enteric-coated and of porcine origin; Creon in 52% (*Abbott, Solvay Pharma*); Panzytrat in 32% (*Tramedico, Aptalis Pharma*); and Pancrease in 16% (*Janssen-Cilag*). Eighty-five percent used a high dose preparation (25,000 FIP-E units of lipase). Twenty-four patients (26%) took the enzymes before their meal, 62 (68%) during the meal, and 11 (12%) after the meal. Forty-nine patients (54%) reported to take additional enzymes when they had a snack.

Table 2. Type of surgical procedure in the 91 operated patients with chronic pancreatitis and pancreatic cancer

	Chronic pancreatitis N=54	**Pancreatic cancer** N=37
Type of surgical procedures		
Whipple – no. (%)	20 (37)	31 (84)
Distal pancreatectomy – no. (%)	5 (9)	3 (8)
Pancreatic head resection – no. (%)	14 (26)	1 (3)
Total pancreatectomy – no. (%)	-	2 (5)
Type of drainage procedures		
Pancreaticojejunostomy – no. (%)	8 (15)	-
Other drainage procedures – no. (%)	7 (13)	-

After surgery, the reported median enzyme dose was 6 capsules per day and 23 patients (25%) took 3 or less capsules per day (Table 3). There was no difference in dosing between the subgroups of patients who had undergone a pancreatic resection and a drainage procedure. Despite treatment, 62 cases (68%) reported steatorrhea-related complaints and 36 (39%) suffered from weight loss. From the patients who took 3 or less capsules per day, 16 (70%) suffered from steatorrhea and 11 (48%) from weight loss, versus 46 (51%) and 23 (34%) of the patients who used more than 3 capsules per day (p-value 0.769 and 0.219, respectively). Only 33 patients (36%) reported to have visited a dietician for their exocrine insufficiency and 44 patients (48%) kept an unnecessary dietary fat restriction, either prescribed by a physician or dietician, or self-imposed. All these results were comparable to the results of the non-operated patients.

Table 3. Treatment outcome of enzyme replacement therapy in 91 surgically treated patients with chronic pancreatitis and pancreatic cancer and 91 non-operated patients

		Operated patients			**Non-operated patients**
		All N=91	**Chronic pancreatitis** N=54 (59%)	**Pancreatic cancer** N=37 (41%)	**All** N=91
Enzyme dose/day*[1];	25% of pts	≤ 3	≤ 4	≤ 3	≤ 3
	50% pts	≤ 6	≤ 6	≤ 5	≤ 4
	75% of pts	≤ 8	≤ 8	≤ 7	≤ 6
Sympt. of steatorrhea – no. (%)		62 (68)	37 (69)	25 (68)	61 (67)
Weight loss – no. (%)		36 (39)	19 (35)	17 (46)	35 (39)
Fat restriction – no. (%)		44 (48)	28 (52)	16 (43)	52 (57)
Referral to dietician – no. (%)		33 (36)	14 (26)	19 (51)	21 (23)

* Number of enteric coated capsules containing 25,000 FIP-E units of lipase

DISCUSSION

This study is the first to capture how postoperative patients with exocrine insufficiency are being treated and gives an insight in the clinical practice of pancreatic enzyme supplementation. The results imply that, even in countries with a well-organized health care system, the majority of patients are under-treated.

Although steatorrhea-related symptoms may correlate poorly with the objective measure of steatorrhea, we believe we have gathered some valid data. Despite enzyme replacement, most patients were still bothered by steatorrhea-related complaints, although studies have shown that adequate enzyme therapy can relieve these symptoms completely. Furthermore, guidelines stress that with the proper amount of enzymes, patients should be able to maintain a normal diet. In our study population, most patients were not aware of this and tended to avoid fat. Interestingly, results were equally poor for non-operated patients.

Apparently, surgeons as well as gastroenterologists fail to achieve a satisfactory treatment response in many of their patients. This poor outcome may be explained by the particular intricacies of pancreatic enzyme replacement therapy. The enzyme dose needs to be individually adjusted, based on the residual pancreatic function and the dietary fat intake[20-27]. In addition, after surgery, the altered anatomy should be taken into account. This variability in individual dosage response, and the lack of practice guidelines, make it difficult for physicians to prescribe the proper dose. Also, publications on this subject are scarce, and therefore, physicians are not well informed.

Furthermore, besides theoretical knowledge, effective treatment requires ample diligence of the treating physician to train patients in flexible dosing. However, enzyme supplementation may not seem a major concern in patients with chronic pancreatitis who are treated for severe pain. Moreover, in case of a life threatening condition such as pancreatic cancer, treatment of exocrine insufficiency may seem futile. Yet, even in these patients, steatorrhea-related symptoms and associated weight loss can be a tremendous burden. A randomized trial by Bruno et al. proved that treatment of exocrine insufficiency is beneficial in such patients. Twenty-one patients with exocrine insufficiency were treated for 8 weeks with either 6 capsules of a high-dose pancreatic enzyme preparation per day, or a placebo[16]. All patients received dietary consultation. A significant difference in body weight was observed; patients on pancreatic enzymes gained 1.2% (0.7 kg), whereas patients on placebo lost 3.7% (2.2 kg). In addition, the fat absorption coefficient in patients on pancreatic enzymes improved by 12%, whereas in placebo patients it dropped by 8%. Also, guidelines published in Gut have recommended that pancreatic enzymes should be used in exocrine insufficient patients with pancreatic cancer, to maintain weight and increase their quality of life[28].

The anatomical changes resulting from pancreatic surgery require careful consideration in the diagnosis and treatment of maldigestion[29]. First of all, the extent of the pancreatic resection is an important denominator for the development of exocrine insufficiency. In addition, the normal digestive physiology is altered in case of reconstructive surgery after a Whipple's procedure. This may lead to a reduction in exocrine pancreatic secretion, due to abnormal postprandial CCK release. Also, asynchrony between gastric emptying and pancreatic secretion in the small intestinal lumen may develop, resulting in improper mixing of enzymes and chyme, a phenomena called secondary exocrine insufficiency[30]. Furthermore, changes in gastric and duodenal acidity may influence the denaturation of enzymes and the dissolution of enteric-coated mini-dose units. Finally, after surgery, in particular after a Roux-en-Y anastomosis or pancreaticoduodenectomy, malabsorption may develop, due to bacterial overgrowth.

Although studies have shown different gastric emptying profiles after conventional and pylorus preserving pancreatoduodenectomy, long-term results have shown that enzyme replacement therapy with enteric-coated preparations is effective post-surgically[31-33]. Therefore, the pancreatic function should be evaluated postoperatively. A fecal Elastase-1 test should be routinely performed, also in asymptomatic patients, because clinical signs of steatorrhea may be absent, as patients tend to limit fat intake to reduce symptoms. Pancreatic enzyme supplementation should be considered in every patient with proven exocrine insufficiency, irrespective of the underlying disease or prognosis. Even in the case of asymptomatic exocrine insufficiency treatment is indicated, because studies have shown that malnutrition may develop in these patients. Moreover, enzymes can also be effective in patients with clinical signs of malabsorption without proven exocrine insufficiency, because secondary exocrine insufficiency may be present.

There are very few studies that address how pancreatic enzyme replacement therapy should be dosed. Only one randomised trial has compared the efficacy of a fixed enzyme dosage to self-administration ad libitum according to fat intake in exocrine insufficient patients with chronic pancreatitis[34]. There was a significant increase from 5 capsules per day during the fixed treatment period to 11 capsules per day during the self-administration period. With this increased dose, a significant decrease in steatorrhea-related symptoms was observed. The authors concluded that efficacy is higher when enzymes are self-dosed by patients in a flexible manner.

Despite the absence of an easy method to establish the adequate dose of pancreatic enzymes, some guidelines can be given. A reasonable starting dose is 50,000 to 75,000 units of lipase for a main meal and 25,000 units for snacks. Subsequently, patients should be instructed to vary the dose according to their dietary fat intake, up to a maximum of 16 capsules a day. They should be explained that the presence of steatorrhea-related symptoms and weight loss imply an insufficient dose of enzymes that needs to be increased. The timing of the capsule ingestion

is also important, because the enzymes have to be mixed with the chyme to be effective. Patients should be instructed to take the enzymes during, or right after a meal[20, 35-38]. Finally, management of exocrine insufficiency can be greatly facilitated by dietary counselling from a well-trained, specialized dietician. A dietician can teach patients the principles of flexible dosing and prevent them from keeping unnecessary dietary restrictions, because many patients tend to avoid fat out of fear for steatorrhea-related complaints.

When treatment response remains unsatisfactorily despite optimal use of enzymes, other steps may be needed. To improve therapeutic efficacy, inhibition of gastric secretion (if gastric acid secretion is preserved) can be attempted by the administration of a proton pump inhibitor. Also, capsules can be opened prior to ingestion, or uncoated enzyme preparations can be prescribed, as accelerated gastric emptying may prevent timely dissolution. If the patient still does not have a satisfactory treatment response, testing for bacterial overgrowth and celiac disease should be considered.

Our study was bound to certain limitations. First of all, due to the design as an anonymous survey, which was required by the medical ethical committee, certain information about the patient population was unavailable. Therefore, we were unable to calculate the response rate, to provide information about the lifestyle of patients, and the aetiology and severity of the pancreatitis or pancreatic cancer. Furthermore, data could not be objectified in case of remaining questions or uncertainties. For example, the outcome measure of weight loss could have been influenced by other factors, such as the underlying malignancy. Finally, a selection bias might have occurred. After all, this survey was distributed amongst members of a patient organization, who are generally highly motivated and better informed. Also, complex pancreatic surgery is mainly executed in tertiary referral centres, where treating physicians are likely to be more experienced in diagnosing and treating exocrine insufficiency. However, if this would be the case, it only stresses our conclusions, as results elsewhere are expected to be even worse.

This is the first study to give insight in the daily practice of pancreatic enzyme usage in patients with exocrine insufficiency after pancreatic surgery. Our results indicate that a substantial proportion of patients are under-dosed and that there is ample room for improvement. To accomplish this, physicians should be attentive on treating exocrine insufficiency, also in patients with an unfavorable prognosis. Patients should be better educated in using pancreatic enzymes in a flexible manner, depending on their meal composition. For this, involvement of a well-trained, specialized dietician is desirable.

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Chapter 5 *The prevalence of fat-soluble vitamin deficiencies and a decreased bone mass in patients with chronic pancreatitis*

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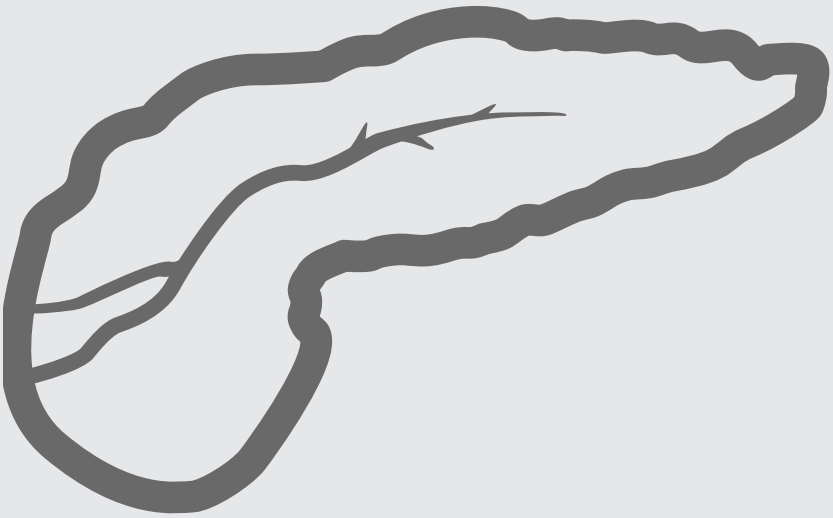

ABSTRACT

Introduction

In chronic pancreatitis, malabsorption of fat is common due to loss of exocrine function. Consequently, these patients are at risk to acquire deficiencies of the fat-soluble vitamins, which may result in a decreased bone mineral density (BMD) and the development of osteopenia and osteoporosis.

Methods

We prospectively enrolled all patients diagnosed with chronic pancreatitis, who visited our outpatient clinic between March and November 2011. Data were collected regarding demographic characteristics, symptoms, and pancreatic function. Serum concentrations of vitamins A, E, K, and D were determined, and BMD was assessed by means of bone densitometry. Results were analyzed according to pancreatic function status and enzyme use, and compared to reference data, when available.

Results

Forty patients were included (43% female; mean age of 52). Alcohol abuse was the major cause of pancreatitis (50%). Twenty-eight patients were exocrine insufficient (70%), of whom 19 used pancreatic enzymes. Vitamin A, D, E, and K deficiencies were present in 3, 53, 10, and 63% of patients, respectively. Osteopenia and osteoporosis were observed in 45% and 10% of patients. A decreased BMD was more frequently observed than expected, based on reference data, even in exocrine sufficient patients.

Conclusions

Deficiencies of fat-soluble vitamins and a decreased BMD are frequently present in chronic pancreatitis, even in exocrine sufficient patients. Consequently, all patients with chronic pancreatitis should be routinely screened for fat-soluble vitamin deficiencies and a decreased BMD.

Key words: chronic pancreatitis, exocrine pancreatic insufficiency, bone loss, fat-soluble vitamins, pancreatic enzyme supplementation

INTRODUCTION

Chronic pancreatitis is an inflammatory disease, characterized by irreversible destruction of pancreatic tissue, which frequently leads to function loss[1]. In exocrine insufficiency, the pancreas is unable to deliver sufficient quantities of digestive enzymes to the small intestine. Because of a large residual capacity, exocrine dysfunction only becomes apparent when 90% of the pancreatic parenchyma is lost[2, 3].

Exocrine insufficiency causes maldigestion of fat, proteins, and carbohydrates[3-5]. Malabsorption of fat results in steatorrhea, which causes typical symptoms of voluminous and greasy stools, abdominal cramps, and bloating[6]. It also leads to weight loss and malnutrition, which poses patients at risk to develop important nutritional deficiencies, especially of the fat-soluble vitamins (vitamin A, D, E, and K)[7-12]. These deficiencies are associated with serious health problems. A vitamin A deficiency may cause impaired night vision, xerophthalmia, and a decreased immune competence. Vitamin E is important for antioxidant defense, and a shortage may lead to neurological disorders[10]. Vitamin K plays a leading role in the blood coagulation cycle. Less known is its involvement in the calcium binding process of bone tissue, by mediating the carboxylation of osteocalcin. Vitamin D also plays a major role in bone metabolism. It activates the calcium channels and stimulates the formation of calcium binding protein, which promotes gastrointestinal calcium and phosphate uptake. Due to impaired absorption of both vitamin D and K, patients with exocrine insufficiency are likely to develop a decreased bone mineral density, resulting in osteopenia or even osteoporosis[13-18].

Osteoporosis prophylaxis is common practice for other gastrointestinal disorders accompanied by malabsorption, such as celiac and inflammatory bowel disease, but not for chronic pancreatitis. Very few studies have addressed the subject of fat-soluble vitamin deficiencies and low bone density in this patient group. Therefore, we have performed this study, and have evaluated the results according to exocrine pancreatic function status and enzyme use.

METHODS

Patients

In this prospective cohort study, patients with chronic pancreatitis were recruited between March and November 2011 from the outpatient clinic of the department of Gastroenterology of the Erasmus Medical Center (Rotterdam, the Netherlands), which functions as a tertiary referral center. The diagnosis of chronic pancreatitis was based on clinical symptoms and morphological changes (e.g. calcifications and ductal changes); pancreatic functional insufficiency; or both. We included both newly referred patients and patients who were already followed at our clinic.

Exclusion criteria were: age under 18; other diseases causing malabsorption, such as inflammatory bowel disease, celiac disease, and short bowel syndrome; other risk factors for a decreased BMD, e.g. chronic kidney and liver failure, hyperthyroidism, early menopause, hyperparathyroidism, chronic prednisone use (7.5 mg per day for >3 months), and hormonal therapy for prostate or breast cancer; and pregnancy. We did not exclude patients using calcium or vitamin supplements, because we wanted to evaluate an unselected group of patients. All subjects gave their informed consent prior to their inclusion in the study.

Collection of data

Information regarding patient demographics, disease characteristics, and lifestyle factors were collected. Pancreatic endocrine function was evaluated by measuring fasting serum glucose levels and glycated hemoglobin levels, and by collecting data on medication use. The exocrine pancreatic function was determined by measuring faecal elastase-1 levels (FEC; normal value more than 0.200 µg per gram of faeces). For this, patients collected a stool sample at home, which was returned to the hospital by mail. In case of exocrine insufficiency, the daily enzyme dose (recalculated as the number of capsules containing 25,000 FIP units of lipase) was documented. In addition, the presence of weight loss and steatorrhea-related symptoms (bloating; abdominal cramps; bulky, sticky, and fatty stools) were assessed with standardized questions. The levels of the fat-soluble vitamins A, E, D, and K were determined from a venous blood sample. Vitamin A, E and K levels were measured in plasma by high-pressure liquid chromatography[19, 20]. Serum 25(OH)D concentrations were determined by using radioimmunoassay[21]. As vitamin D levels depend on sunlight exposure, we minimized this contributing factor, by not collecting data during wintertime. The bone mineral density was measured by dual-energy X-ray absorptiometry (DEXA). The measurement sites were the lumbar spine (L2 – L4) and the left femur. The results are presented as T score (normal value >-1) and Z score (normal value >-1). The T-score is the number of standard deviations above or below the mean bone density of a healthy 30-year-old adult of the same sex and ethnicity, while the Z-score matches for age, which allows comparing the BMD of patients in different age groups.

Outcome measures

The outcome measures of this study were deficiencies of the fat-soluble vitamins (vitamin A <1.25 µmol/liter; vitamin E <16.5 µmol/liter; 25-(OH)-vitamin D3 <38 pmol/liter; and vitamin K <0.8 nmol/liter) and the presence of a decreased BMD, either osteopenia (T score between -1 and -2.5), or osteoporosis (T score below -2.5). These endpoints were evaluated for three different subgroups: exocrine sufficient patients, exocrine insufficient patients who receive enzyme suppletion, and exocrine insufficient patients who do not use enzymes. The outcomes of bone density were compared to available reference data from the general Dutch population[22-24]. Data on the prevalence of fat-soluble vitamin deficiencies in healthy adults were not available for comparison.

Statistical analyses

Statistical analyses were conducted using SPSS 17.0. Quantitative data were expressed as means ±SD and percentiles. Categorical variables were compared using the Chi-square test or the Fischer exact test, where appropriate. Differences between the groups were considered significant if the p-value was less than 0.05 for a two-tailed test.

RESULTS

Forty-four patients were assessed for this study, of which 40 were included. Three patients were excluded because of kidney failure and one because of hyperthyroidism. The demographics, life-style factors, disease characteristics, and medication use of the study population are described

Table 1. Patient and disease characteristics of 40 patients with chronic pancreatitis

Age in years– mean ± SD	52 ± 11
Female sex – no. (%)	17 (43)
Postmenopausal women – no. (%)	12 (30)
BMI – mean ± SD	24 ± 5
Cause of pancreatitis	
Alcohol – no. (%)	20 (50)
Idiopathic – no. (%)	17 (43)
Other* – no. (%)	3 (7)
Disease duration in yrs – median (IQR)	2 (1 – 4)
Calcifications – no. (%)	20 (69)
Pancreatic surgery** – no. (%)	2 (5)
Current smoker – no. (%)	27 (68)
Ongoing alcohol abuse – no. (%)	1 (3)
Multivitamin usage – no. (%)	4 (10)
Vitamin D usage – no. (%)	6 (15)
Bisphosphonate replacement therapy – no. (%)	0
Warfarin use – no. (%)	0
Endocrine insufficient – no. (%)	18 (45)
HbA1c – median (IQR)	55.5 (46.8 – 62)
Exocrine insufficient – no. (%)	28 (70)
Enzyme replacement therapy – no. (%)	19 (48)
Enzyme capsules per day – median (IQR)	6 (4 – 7)
Duration of enzyme use in months – median (IQR)	6 (2 – 39)

* One patient had an autoimmune related pancreatitis, one a hereditary pancreatitis, and one patient a drug-related pancreatitis

** A pancreatojejunostomy and a distal pancreatectomy

Table 2. Serum levels [median (IQR)] and prevalence of fat-soluble vitamins in patients with chronic pancreatitis, according to pancreatic function and enzyme use

	All patients N = 40 (100%)	**Exocrine sufficient** N = 12 (30%)	**Exocrine insufficient Using enzymes** N = 19 (48%)	**Exocrine insufficient Without enzymes** N = 9 (23%)	***p*-value***
Vitamin levels in all patients					
Vitamin A (normal 1.25 – 3 µmol/l)	1.95 1.60 – 2.51)	1.97 (1.55 – 2.32)	1.96 (1.60 – 2.66)	1.93 (1.45 – 2.59)	
Vitamin E (normal 16.5 – 41.6 µmol/l)	27.1 (20.6 – 33.0)	29.7 (25.5 – 38.7)	25.4 (18.6 – 28.9)	25.4 (17.8 – 31.5)	
Vitamin D (normal 38 – 136 pmol/l)	40 (23 – 85)	74 (28 – 93)	40 (22 – 83)	25 (21 – 74)	
Vitamin K (normal 0.8 – 5.3 nmol/l)	0.6 (0.4 – 0.9)	0.7 (0.3 – 1.0)	0.6 (0.3 – 0.9)	0.5 (0.4 – 2.1)	
Prevalence of fat-soluble vitamins					
Vit A deficiency – no. (%)	1 (3)	0	0	1 (11)	0.257
Vit E deficiency – no. (%)	4 (10)	0	2 (11)	2 (22)	0.340
Vit D deficiency – no. (%)	21 (53)	4 (33)	10 (53)	7 (78)	0.243
Vit K deficiency – no. (%)	25 (63)	7 (58)	13 (68)	5 (56)	0.678

* Fisher's exact Test.

Table 3. Median (IQR) levels of the T and Z score* of the left femur and lumbar spine and the prevalence of a decreased Bone Mass according to pancreatic function and enzyme use

	Dutch Reference Population	**All patients** N = 40 (100%)	**Exocrine sufficient** N = 12 (30%)	**Exocrine insufficient Using enzymes** N = 19 (48%)	**Exocrine insufficient Without enzymes** N = 9 (23%)	***p* value****
Left femur						
T score		-0.9 (-1.68 – -0.2)	- 0.4 (-1.13 – 0.15)	-0.75 (-1.63 – -0.15)	-1.65 (-1.8 – -1.0)	
Z score		-0.2 (-1.0 – 0.58)	0.3 (-0.93 – 0.85)	0.0 (-0.8 – 0.73)	-0.5 (-1.12 – -0.05)	
Lumbar Spine						
T score		-0.65 (-1.25 – 0.58)	-0.5 (-1.2 – 1.1)	-0.4 (-1.1 – 0.8)	-1.05 (-1.75 – -0.18)	
Z score		-0.15 (-0.9 – 0.98)	0.05 (-1.05 – 1.93)	0.15 (-0.83 – 1.07)	-0.55 (-1.0 – 0.83)	
Decreased BMD – no. (%)	(10 – 15%) [22-24]	22 (55)	5 (42)	9 (47)	8 (89)	0.039
Osteopenia – no. (%)	(10%)	18 (45)	4 (33)	7 (37)	7 (78)	0.053
Osteoporosis – no. (%)	(1 – 5%)	4 (10)	1 (8)	2 (11)	1 (11)	1.0
Common bone fractures – no. (%)		16 (40%)	6 (50)	5 (26)	5 (56)	0.361

*T score values: normal BMD > -1; osteopenia -2.5 to -1; osteoporosis < -2.5; Z score values: normal BMD > -1; low/ normal BMD -2.5 to -1; low BMD < -2.5

** Patients in the last column (untreated exocrine insufficiency) were compared to the other two subgroups

in Table 1. Endocrine insufficiency was present in 18 patients (45%). Twenty-eight patients were exocrine insufficient (70%), of whom 19 were treated with enzyme supplementation (48%). Eighteen patients with exocrine insufficiency reported steatorrhea-related complaints (64%), and 8 suffered from weight loss (29%).

The median serum levels and prevalence of the fat-soluble vitamins are shown in Table 2. A vitamin A, E, D, and K deficiency were present in 1 (3%), 4 (10%), 21 (53%), and 25 (63%) patients, respectively. Deficiencies of the vitamins D and K were frequently observed in all subgroups, even in exocrine sufficient patients. There were no significant differences found between the three subgroups. In Table 3 the median T- and Z-scores of the left femur and lumbar spine and prevalence of a decreased BMD are shown. A decreased bone mass was observed in 22 patients (55%), 18 of whom had osteopenia (45%) and 4 osteoporosis (10%). The prevalence of osteopathy's was increased compared to the reference population in all three subgroups, but was significantly higher in patients with untreated exocrine insufficiency than in the joint other two groups (89% vs. 45%, p-value 0.013). Sixteen patients (40%) reported to have had a fracture in the past.

DISCUSSION

The results of this study show that patients with chronic pancreatitis are at risk to develop fat-soluble vitamin deficiencies (especially of the vitamins D and K) and a decreased bone mass. This risk was highest in patients with untreated exocrine insufficiency, but was also increased in those with a normal pancreatic function. We observed that in insufficient patients treated with enzyme supplementation, the prevalence of osteopathy's was comparable to that of patients with a normal pancreatic function. However, the risk remained increased, compared to a reference population.

Besides malabsorption due to steatorrhea, several other factors may have contributed to these findings. First, patients with chronic pancreatitis often have a poor food intake, due to chronic pain. Also, patients tend to avoid fat, out of fear for steatorrhea-related symptoms. In addition, in case of alcoholic pancreatitis, bad lifestyle habits may play a role. Finally, in the development of a decreased bone mass, chronic inflammation may be important, as certain inflammatory mediators are also key players in bone mineral homeostasis[25, 26]. IL-1, IL-6, TNF-α, and IFN-γ for instance were proven to contribute to bone loss in patients with inflammatory bowel disease[27-30].

Unfortunately, exact data regarding the prevalence of fat-soluble vitamin deficiencies in healthy subjects are not available. Therefore, we could not correlate our findings to the general

population. Nevertheless, there is enough evidence to conclude that the prevalence is substantially increased in the study population. Vitamin A and E deficiencies are known to be extremely rare, and generally occur much more sporadic than the 3 and 10% that we observed in this study. Vitamin D deficiency seems to be more common, with a reported prevalence of 10-35% in populations at risk, but this is still much lower than the 52% that we found[31, 32]. In addition, the mean vitamin D level of 40 that we found in our study population is much lower than the values that were observed in other studies. For instance, in a Dutch multi-ethnic population between 18 and 65 years old, a mean value of 67 (50-83) was found[33-35].

In healthy individuals a vitamin K deficiency is rare, while in our study population the majority had a shortage. Moreover, we may have even underestimated vitamin K deficiency in bone. Vitamin K is present in liver and bone, independently. We measured the serum value that represents the liver storage, while bone is more susceptible to shortage[15, 16]. Although vitamin K deficiency was frequently observed, major bleeding problems were not encountered. Therefore, the clinical relevance of this finding remains unclear and should be further evaluated

We observed that a decreased bone mass was much more prevalent in patients with chronic pancreatitis, than in reference populations. However, these reference data were obtained from studies of patients 'at risk', such as postmenopausal women and the elderly. Therefore, the prevalence is likely to be lower in the general population, which only stresses our conclusion, that osteopathy's are more common in patients with chronic pancreatitis.

To date, only a few small and retrospective studies have been published on the subject of vitamin deficiencies in chronic pancreatitis. In the early eighties, Dutta et al. showed that exocrine insufficient patients often lack fat-soluble vitamins, despite enzyme treatment. Fifteen patients were evaluated, and a vitamin A, D, E, and K deficiency were present in 47, 67, 67, and 13% of patients. They also demonstrated that the use of vitamin supplements corrected these deficiencies[10]. Another study measured serum levels of the vitamins A and E in 41 patients with chronic pancreatitis, of whom 58% suffered from steatorrhea, and observed a vitamin A deficiency in 16% and a vitamin E deficiency in 75% of patients[36]. We found these two deficiencies to be much more rare, perhaps because the majority of their cohort was underweight and malnourished, which was not the case in our population. The scarce literature on vitamin K deficiencies in pancreatic disease shows a prevalence of 30 to 80% in the liver and 50% in bone[37, 38], which our findings confirmed. Recently, Dominguez-Munoz et al. showed that patients with exocrine insufficiency, both with and without steatorrhea-related symptoms, suffered from nutritional deficiencies, which were restored by adequate enzyme supplementation[39]. This seems to be supported by our results, as we observed less vitamin deficiencies and bone loss in patients treated with enzyme suppletion.

Several studies have reported that chronic pancreatitis patients have an increased risk to develop significant bone loss[17, 18, 40]. In 2008, 73 patients were prospectively evaluated; osteopenia was present in 26% and osteoporosis in 5% of cases[41]. Sudeep et al. compared 31 men with nonalcoholic chronic pancreatitis with 35 controls and found a decreased bone mineral density in 29% of study patients, as compared to 9% in controls[42]. Of course, from a clinical perspective, fracture rate is the most relevant parameter. In our population, the prevalence of common fractures was 40%, which is high compared to the 25% rate, observed in the British population[43]. Although this was never prospectively evaluated in chronic pancreatitis patients, a similar rate of 41% was observed in primary biliary cirrhosis patients, who are also at risk for malabsorption[44]. In addition, Tignor et al. performed a retrospective cohort study in 3194 patients with chronic pancreatitis, and found that in a period of 10 years, the fragility fracture prevalence was greater than controls (4.8 vs. 1.1) and comparable with, or higher than patients with celiac (5.0) or Crohn's disease (3.0), for whom metabolic bone disease screening is already recommended[45].

Our results imply that clinicians should be more alert on the presence of fat-soluble vitamin deficiencies and a decreased BMD in patients with chronic pancreatitis. They also justify that these patients should be routinely screened for fat-soluble vitamin deficiencies, regardless of their pancreatic function status. In addition, we recommend bone mineral density measurement by means of a DEXA-scan, which should be repeated at regular intervals (for instance, every two years). Furthermore, to prevent malnutrition and malabsorption, patients with exocrine insufficiency should be properly treated with a sufficient quantity of pancreatic enzymes[46-48]. We also believe that patients should be referred to a dietician, to promote a normal dietary fat intake. Finally, prescribing vitamin supplements can be considered[10, 38, 49].

To our knowledge, this is the first study that prospectively evaluated the vitamin and bone status of patients with chronic pancreatitis, and made a distinction between patients with a normal exocrine function and those with exocrine insufficiency, with or without pancreatic enzyme supplementation. Our study had certain limitations. We only evaluated cases, and did not compare our results to a formal age- and sex-matched control group. Furthermore, we included a heterogeneous group of patients in different disease and treatment stages. Our study cohort was too small to compare the prevalence in vitamin deficiencies between the three subgroups. This means that only a large effect would have been found significant. Furthermore, pain caused by chronic pancreatitis could have reduced dietary intake in some patients, resulting in decreased vitamin levels. Unfortunately, due to the design of our study we did not assess the daily dietary vitamin intake. In addition, we did not measure bone specific vitamin K, which could have supplied more reliable information regarding the vitamin K status. Finally, we may have underestimated our results by including patients using vitamin

and calcium supplements and by carrying out the study in a specialized center, where treating physicians are more experienced in treating chronic pancreatitis.

The present study shows that deficiencies of the fat-soluble vitamins and a decreased BMD are frequently seen in chronic pancreatitis, even in exocrine sufficient patients. Therefore, these patients should be routinely screened for fat-soluble vitamin deficiencies, and undergo a bone densitometry at regular intervals. In case of exocrine insufficiency, patients should receive appropriate patient-tailored treatment with pancreatic enzymes to abolish fat malabsorption. In addition, patients with vitamin deficiencies should be adequately supplemented, and osteopathy's should be treated according to existing guidelines.

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Chapter 6

A prospective assessment of the natural course of the exocrine pancreatic function in patients with a pancreatic head tumour

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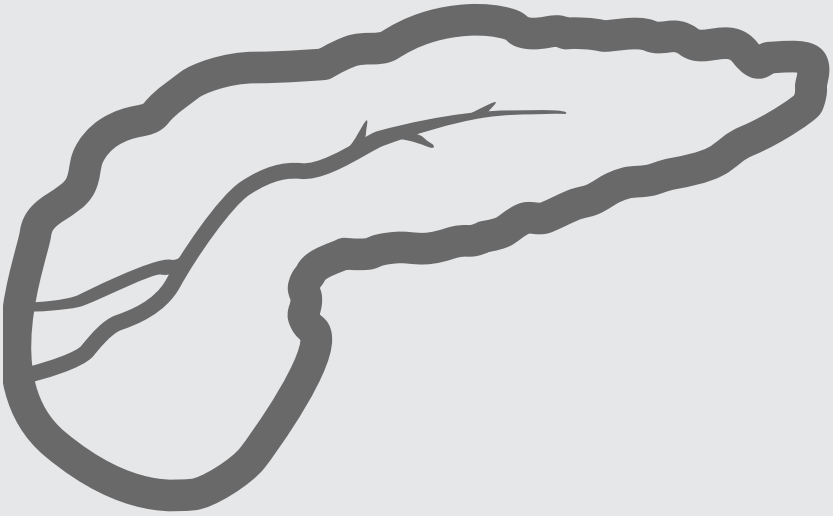
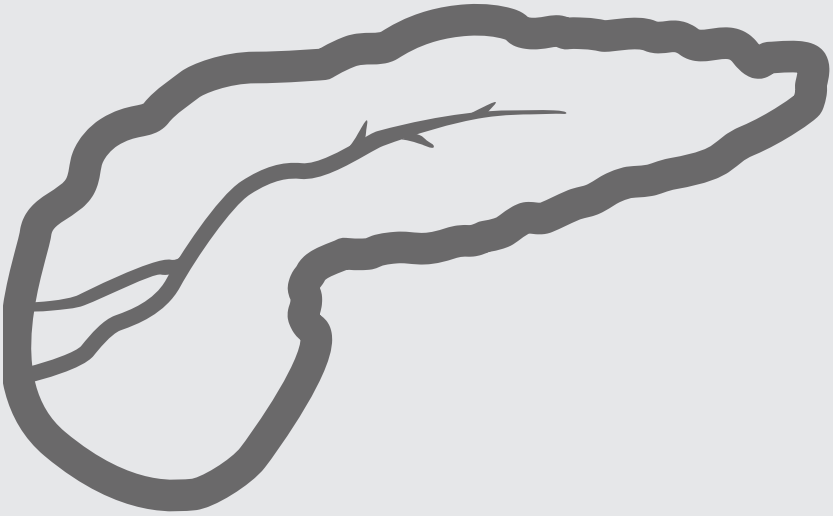


Chapter 7

A prospective assessment of the influence of pancreatic cancer resection on exocrine pancreatic function

Edmée C.M. Sikkens, Djuna L. Cahen, Jill de Wit,
Caspar W.N. Looman, Casper van Eijck, Marco J. Bruno

Submitted

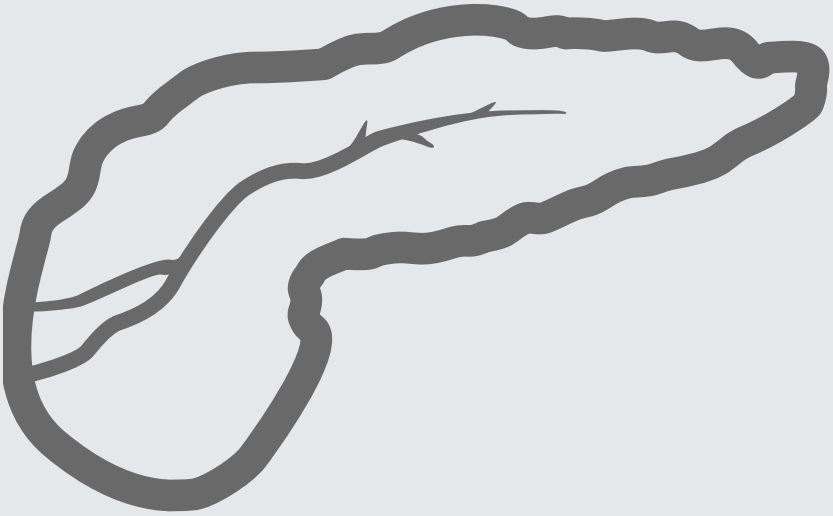


Chapter 8

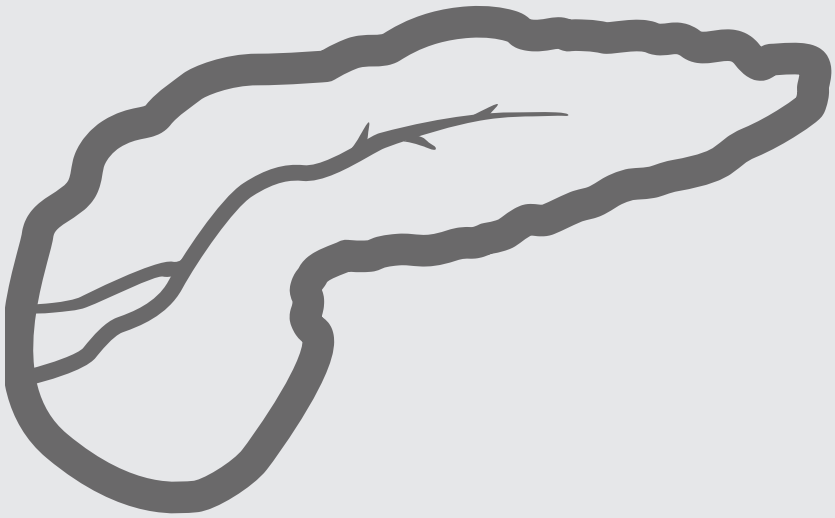
Exocrine insufficiency in chronic pancreatitis; flexible dosing of pancreatic enzymes improves clinical treatment outcome

Edmée C.M. Sikkens, Djuna L. Cahen, Jill de Wit, Caspar W.N. Looman, Frank J.G.M. Kubben, Marco J. Bruno

Submitted.



Chapter 9 *Summary and Conclusions*



SUMMARY

This thesis concerns the clinical implications and treatment of exocrine pancreatic insufficiency in patients with chronic pancreatitis and pancreatic cancer. Treating exocrine insufficiency is challenging, because the optimal enzyme dose varies, depending on the remaining pancreatic function, potential changes in anatomy and digestive physiology, and the dietary fat content. Unfortunately, physicians are not always aware that the efficacy of enzyme replacement therapy depends on these factors. Moreover, in cancer patients, exocrine insufficiency is frequently overlooked, because the primary focus is directed on treating the underlying disease.

Chapter 2 provides a systematic review on exocrine insufficiency in patients with chronic pancreatitis. It explains the (patho)physiology, gives an overview of the available diagnostic tests, and discusses the difficulties of treatment with pancreatic enzymes.

To evaluate the common practice of enzyme treatment, we performed an anonymous survey in patients with chronic pancreatitis **(chapter 3)** and patients who underwent pancreatic surgery **(chapter 4)**. The surveys were distributed to members of the Dutch and German associations of patients with pancreatic disorders. They focussed on enzyme use, steatorrhea-related symptoms, consultation with a dietician, and food restrictions. In both surveys, the majority of patients (70%) reported steatorrhea-related symptoms, despite enzyme supplementation (median of 6 capsules per day). Also, patients were rarely referred to a dietician for dietary and treatment instructions. These results imply that exocrine insufficiency is often under-treated, even in countries with a well-organized health care system.

To evaluate the consequences of under-treatment of exocrine insufficiency on the nutritional status, we assessed the prevalence of fat-soluble vitamin deficiencies and a decreased bone mass in patients with chronic pancreatitis **(chapter 5)**. Vitamin A, D, E, and K deficiencies were present in 3, 53, 10, and 63% of patients, respectively. A decreased bone mass was more frequently observed than expected, based on reference data, even in exocrine sufficient patients. Therefore, chapter 4 concludes that the vitamin and bone status should be routinely checked in all chronic pancreatitis patients.

In pancreatic cancer, exocrine insufficiency is a well-documented complication. The dismal survival of this disease is finally showing some improvement due to novel (neoadjuvant) treatment regimens. Therefore, treating exocrine insufficiency and preventing malabsorption and malnutrition is of increasing importance, to keep patients in an optimal condition. We prospectively assessed the course of the exocrine function in patients with an inoperable tumour of the pancreatic head region, to evaluate the natural course of the pancreatic exocrine function **(chapter 6),** and after resective surgery, to evaluate the influence of a surgical resection

(chapter 7). Each month, the exocrine function was determined with a faecal elastase-1 test. Endocrine function, steatorrhea-related symptoms, and body weight were also evaluated. In both studies, patients were followed for 6 months, or until death.

In the inoperable patient group, 66% of patients were exocrine insufficient at diagnosis, which increased to 92% after a median follow-up of 2 months. In the operated patient group, 45% was exocrine insufficient at diagnosis. Six months later, this had increased to 89%. These results indicate that the presence of a tumour in the pancreatic head region almost inevitably leads to exocrine functional impairment. Resection of the tumour with restoration of the ductal patency does not seem to alter this course.

In the final chapter of this thesis (**chapter 8)** we prospectively evaluated if extensive patient-education regarding flexible self-dosing improves treatment outcome in exocrine insufficient patients with chronic pancreatitis. Patients were instructed to adjust the enzyme dose according to their dietary fat intake and presence of steatorrhea-related symptoms. With flexible dosing, the mean enzyme dose increased significantly, from 3 to 10 capsules per day. This lead to a significant improvement of steatorrhea-related symptoms and BMI (p-values < 0.001), an effect that persisted on the longer-term. Obviously, patient-education in flexible dosing is a way to improve treatment efficacy and should be routinely applied in enzyme supplementation therapy.

GENERAL CONCLUSION AND FUTURE DIRECTIONS

In conclusion, many exocrine insufficient patients are under-treated by an inadequate and fixed enzyme dose, or by being deprived from supplementation therapy all together. As this has serious implications on the nutritional status, with vitamin deficiencies and osteoporosis as a result, treatment needs to be improved.

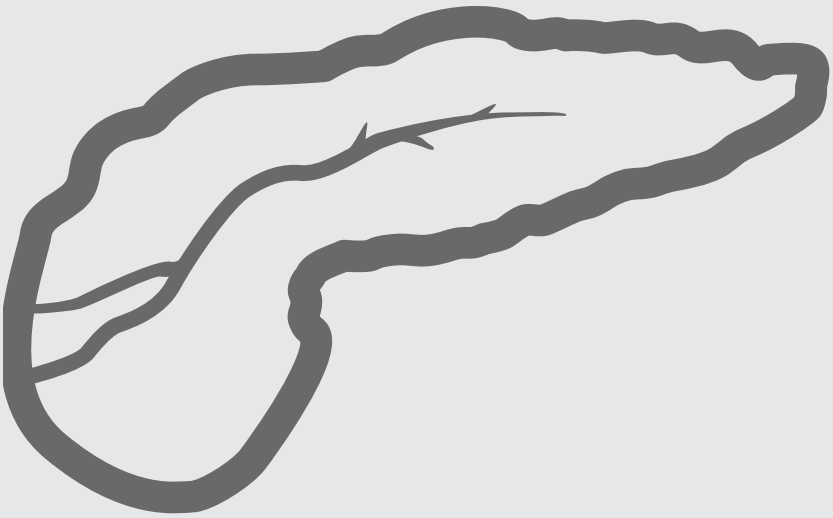
Physicians should be attentive to diagnosing exocrine insufficiency, especially in patients with chronic pancreatitis and pancreatic cancer. As exocrine insufficiency appears to be so common in pancreatic cancer, enzyme supplementation should be routinely considered at diagnosis, in both operable and inoperable patients, in order to endure burdensome treatments and possibly even to improve their outcome. If treatment is initiated, the enzyme dose needs to be individually tailored and adjusted to the dietary fat intake in a flexible manner. Physicians should educate their patients regarding these principles with the help of an experienced dietician, as proper instructions improve treatment outcome. Patients with pancreatic disease should be routinely screened for fat-soluble vitamin deficiencies and a decreased bone mass. In order

to assist both physicians and dieticians in treating this complex illness, specified treatment guidelines would be helpful.

Future studies should focus on further improving the treatment outcome of enzyme supplementation. To establish the true benefits of flexible self-dosing, larger, preferably randomized trials are needed. Also, it would be interesting to investigate if flexible self-dosing can prevent long-term complications, such as fat-soluble vitamin deficiencies and osteoporosis. Another way to improve treatment outcome is to develop enzyme preparations that are less sensitive to proteolytic degeneration, resulting in a higher intraduodenal lipolytic activity. For this, bacterial lipase and lipase produced with the help of gene therapy seem to be promising developments.

In addition, as the prognosis of pancreatic cancer is gradually improving, future studies should evaluate the role of enzyme supplementation in these patients. Prospective studies should establish if enzyme supplementation has a positive effect on survival. Also, the pancreatic function in long-term survivors, several years after surgery, may be investigated.

Samenvatting en Conclusies



SAMENVATTING

De studies in dit proefschrift betreffen de klinische implicaties en therapie van exocriene pancreasinsufficiëntie. De behandeling van exocriene insufficiëntie is ingewikkeld, omdat de optimale enzymdosis varieert per patiënt. Deze wordt bepaald door de resterende pancreasfunctie, potentiële veranderingen in de anatomie en intestinale fysiologie, en door het vetgehalte van de voeding. Blijkbaar zijn artsen zich niet altijd bewust van deze variabiliteit. Bovendien wordt bij patiënten met een pancreascarcinoom de aanwezigheid van exocriene insufficiëntie vaak over het hoofd gezien, omdat de onderliggende ziekte alle aandacht vergt.

Hoofdstuk 2 geeft een algemeen overzicht van de implicaties van exocriene insufficiëntie voor patiënten met chronische pancreatitis. Naast het beschrijven van de (patho)fysiologie, worden beschikbare diagnostische technieken besproken. Verder wordt er ingegaan op de problematiek van behandeling met pancreasenzymen.

Om een beeld te krijgen van pancreasenzym gebruik in de praktijk, hebben wij een anonieme enquête uitgevoerd bij patiënten met chronische pancreatitis **(hoofdstuk 3)** en patiënten die pancreas chirurgie ondergingen **(hoofdstuk 4)**. De vragenlijsten werden verstuurd aan leden van de Nederlandse en Duitse vereniging van patiënten met pancreas gerelateerde ziekten. De vragen betroffen enzym gebruik, steatorroe gerelateerde klachten, eventuele verwijzing naar een diëtist, en dieet beperkingen. In beide groepen bleek de meerderheid van de patiënten steatorroe gerelateerde klachten te hebben (70%), ondanks gebruik van enzymen (mediaan 6 capsules per dag). Verder werden patiënten nauwelijks doorverwezen naar een diëtist. Deze resultaten tonen aan dat de behandeling van exocriene insufficiëntie vaak onvoldoende is, zelfs in landen met een goed georganiseerde gezondheidszorg.

Hoofdstuk 5 inventariseert de consequenties van een eventueel tekortschietende behandeling van exocriene insufficiëntie op de voedingstoestand. Hiervoor bepaalden wij de prevalentie van vet-oplosbare vitamine deficiënties en een verminderde botmassa bij patiënten met chronische pancreatitis. Een vitamine A, D, E en K deficiëntie werden vastgesteld bij 3, 53, 10, en 63% van de patiënten. Een verminderde botmassa kwam vaker voor dan verwacht, vergeleken met een gezonde referentie populatie, zelfs bij patiënten met een normale pancreasfunctie. Wij kwamen daarom tot de conclusie dat de vitamine en bot status regelmatig gecontroleerd moeten worden bij alle patiënten met chronische pancreatitis.

Bij pancreascarcinoom is exocriene insufficiëntie een vaak voorkomende complicatie. De overlevingskans van deze ziekte is geleidelijk verbeterd als gevolg van nieuwe (neo)adjuvante behandelstrategieën. Hierdoor is een goede lichamelijke conditie en het voorkomen van malabsorptie door exocriene insufficiëntie van toenemend belang geworden. Wij vervolgden

prospectief de exocriene functie bij patiënten met een inoperabel pancreas carcinoom, om het natuurlijke beloop vast te leggen **(hoofdstuk 6),** en bij geopereerde patiënten, om het effect van tumor resectie te beoordelen **(hoofdstuk 7).** Iedere maand werd de exocriene functie bepaald met behulp van een faeces elastase-1 test. Daarnaast werden de endocriene functie, steatorroe gerelateerde klachten en lichaamsgewicht beoordeeld. Patiënten werden gevolgd gedurende 6 maanden of tot hun overlijden.

In de groep patiënten met een inoperabele tumor was bij het stellen van de diagnose 66% exocrien insufficiënt. Na een mediane follow-up van 2 maanden was dit percentage opgelopen tot 92%. Bij de geopereerde patiëntengroep was ten tijde van de diagnose 45% exocrien insufficiënt en zes maanden later 89%. Deze resultaten impliceren dat de aanwezigheid van een pancreascarcinoom vrijwel altijd leidt tot exocriene dysfunctie. Resectie van de tumor met herstel van de afvloed van pancreas sappen lijkt deze uitkomst niet te beïnvloeden.

In het laatste hoofdstuk van dit proefschrift **(hoofdstuk 8)** evalueerden wij prospectief of educatie van patiënten met chronische pancreatitis in het flexibel zelf-doseren van pancreasenzymen de behandeluitkomst verbeterd. Patiënten werden geïnstrueerd om hun enzymdosis aan te passen op basis van de hoeveelheid vet in hun voeding en de aanwezigheid van steatorroe gerelateerde klachten. Tijdens het flexibel doseren nam de gemiddelde enzymdosis significant toe, van 3 naar 10 capsules per dag. Dit leidde tot een significante verbetering van de steatorroe gerelateerde klachten en een toename van de BMI (beide p-waardes < 0.001), een effect dat ook op de lange termijn stand hield. Blijkbaar is patiënteducatie in flexibel doseren een goede manier om de effectiviteit van de behandeling te verbeteren en dus adviseren wij dit standaard toe te passen.

ALGEMENE CONCLUSIE EN AANBEVELINGEN VOOR IN DE TOEKOMST

Dit proefschrift toont aan dat veel patiënten met exocriene insufficiëntie onderbehandeld worden met een onjuiste en vaste enzymdosis, of zelfs helemaal geen enzymen krijgen voorgeschreven. Aangezien dit ernstige gevolgen heeft voor de voedingstoestand (met vitamine deficiënties en osteoporose als resultaat), is het belangrijk deze behandeling te verbeteren.

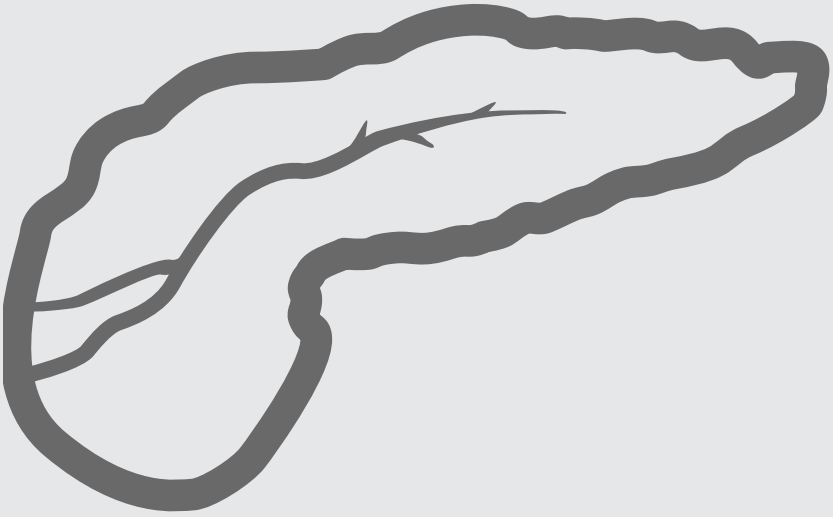
Allereerst moeten artsen voldoende aandacht besteden aan het diagnosticeren van exocriene insufficiëntie. Bij patiënten met een pancreascarcinoom kan zelfs overwogen worden routinematig enzymsuppletie voor te schrijven, aangezien het ontwikkelen van exocriene dysfunctie bij deze patiënten vrijwel onvermijdelijk lijkt. Dit zou een positieve bijdrage kunnen leveren aan het ondergaan van de zware behandelingen, en zo mogelijk zelfs het ziekteverloop verbeteren.

Wanneer behandeling met enzym suppletie gestart wordt, moet de dosis individueel worden bepaald en flexibel aangepast op geleide van de hoeveelheid vet in het dieet. Artsen moeten hun patiënten hier uitgebreid over informeren. De hulp van een gespecialiseerde diëtist is daarbij onontbeerlijk. Om artsen en diëtisten bij deze complexe taak te ondersteunen, zouden duidelijke behandelrichtlijnen van toegevoegde waarde zijn.

Toekomstige studies zouden zich moeten richten op het verbeteren van de behandeling van exocriene insufficiëntie. Om definitief het voordeel van flexibel zelf-doseren van enzymen aan te tonen, zijn grotere, en bij voorkeur gerandomiseerde studies nodig. Daarnaast zou het interessant zijn te onderzoeken of flexibel zelf-doseren lange termijn complicaties kan voorkomen, zoals deficiënties van de vetoplosbare vitaminen en osteoporose. Een andere manier om de behandeling te verbeteren, is enzym preparaten te ontwikkelen die minder gevoelig zijn voor proteolytische degeneratie, resulterend in een hogere intraduodenale lipolytische activiteit. Hiervoor lijken bacteriële lipase en lipase geproduceerd met behulp van gen therapie, veel belovend.

Tot slot, aangezien de prognose van pancreascarcinoom lijkt te verbeteren, zou de rol van enzymsuppletie bij deze patiënten verder geëvalueerd moeten worden. Prospectieve studies zijn nodig om te vast te stellen of enzymsuppletie een positief effect heeft op de overleving. Daarnaast zou de pancreasfunctie op de lange termijn moeten worden onderzocht bij patiënten die een aantal jaar na operatie nog in leven zijn.

List of publications



LIST OF PUBLICATIONS

1. **ECM Sikkens**, DL Cahen, EJ Kuipers, MJ Bruno
   Pancreatic enzyme replacement therapy in chronic pancreatitis
   Best practice and Research Clinical Gastroenterology 2010;24(3):337-347.

2 **ECM Sikkens**, DL Cahen, C van Eijck, EJ Kuipers, MJ Bruno
   Patients with exocrine insufficiency due to chronic pancreatitis are undertreated; a Dutch national survey
   Pancreatology 2012;12(1):71-3.

3. **ECM Sikkens**, DL Cahen, C van Eijck, EJ Kuipers, MJ Bruno
   The daily practice of pancreatic enzyme replacement therapy after pancreatic surgery, a northern European survey
   Journal of Gastrointestinal Surgery 2012;16(8):1487-92.

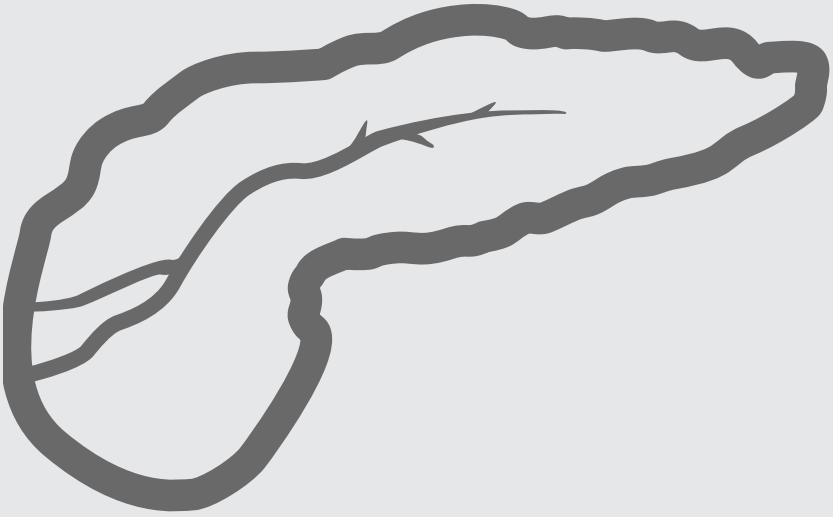
4. **ECM Sikkens**, DL Cahen, AD Koch, H Braat, J Poley, EJ Kuipers, MJ Bruno
   The prevalence of fat-soluble vitamin deficiencies and a decreased bone mass in patients with chronic pancreatitis
   Pancreatology 2013;13(3): 238-242.

5. **ECM Sikkens**, DL Cahen, J de Wit, CWN Looman, C van Eijck, MJ Bruno
   A prospective assessment of the natural course of the exocrine pancreatic function in patients with a pancreatic head tumour
   Journal of Clinical Gastroenterology 2013. *In press.*

6. **ECM Sikkens**, DL Cahen, J de Wit, CWN Looman, C van Eijck, MJ Bruno
   A prospective assessment of the influence of pancreatic cancer resection on exocrine pancreatic function
   Status: submitted.

7. **ECM Sikkens**, DL Cahen, J de Wit, CWN Looman, MJ Bruno
   Exocrine insufficiency in chronic pancreatitis; flexible dosing of pancreatic enzymes improves clinical treatment outcome
   Status: submitted.

Dankwoord



DANKWOORD

De afgelopen 4 jaar zijn voor mij een interessante en leerzame periode geweest. Ik heb mooie kansen gekregen en benut, wat niet altijd zonder slag of stoot is gegaan. Zonder de hulp en steun van velen, was mijn promotietraject dan ook niet tot stand gekomen. Kortom, een aantal mensen verdienen een speciaal woord van dank.

Allereerst, mijn promotor, prof. dr. M.J. Bruno. Beste Marco, ik kan mij nog goed herinneren, dat ik uitermate enthousiast mijn allereerste abstract aan jou overhandigde. Je bladerde ietwat verbijsterd door het stapeltje papieren en vroeg mij vriendelijk, waar het abstract dan was. Toen werd mij duidelijk dat 2800 characters niet hetzelfde zijn als 2800 woorden. De afgelopen 4 jaar heb ik veel respect gekregen voor jouw passie en talent op het gebied van onderzoek. Van jouw kritische en analytische blik op mijn studies heb ik veel geleerd. Hierdoor is mijn proefschrift zeker naar een hoger niveau getild.

Co-promotor dr. D.L. Cahen. Beste Djuna, ik was nog maar een half jaar bezig met mijn promotie, toen jij mijn co-promotor werd. Ik weet nog goed, dat Marco zei, dat jij als getalenteerd schrijfster mij veel kon leren. Niets is minder waar gebleken. Ik heb bewondering voor jouw enorme gedrevenheid en toewijding voor de wetenschap. Naast de ene dag dat jij werkzaam bent in Rotterdam, heb jij veel tijd voor mij vrij gemaakt. Zonder jouw inzet had ik dit eindresultaat niet zo snel kunnen bereiken. Dankjewel daarvoor!

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Gedurende mijn promotie ben ik door een aantal mensen met hun organisatorisch talent enorm geholpen: lieve Henny, wat kon ik toch altijd genieten van al jouw mapjes, die orde schepten in de chaos. Lieve Carla, geen afspraak met Marco zonder jou! Dank voor al jullie hulp en de prettige samenwerking de afgelopen 4 jaar. Berna en Andrea, ook jullie beiden wil ik hartelijk bedanken voor alle hulp en gezelligheid.

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Een speciaal woord voor mijn nimfjes:

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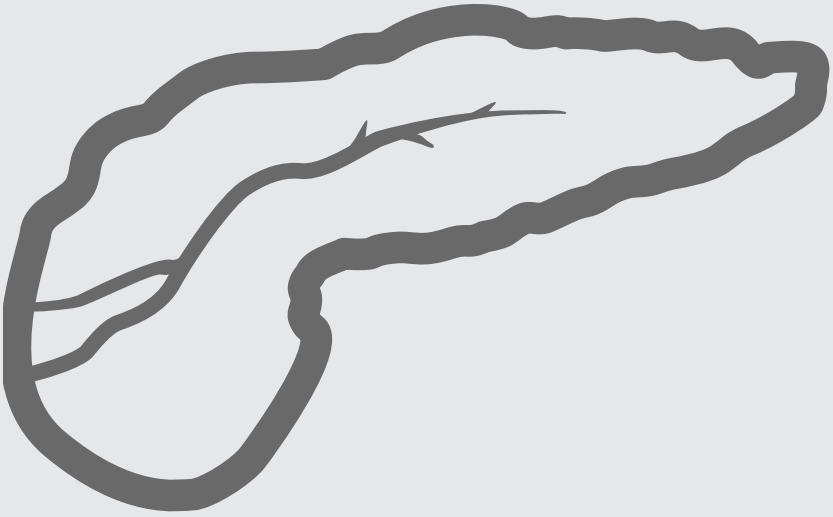
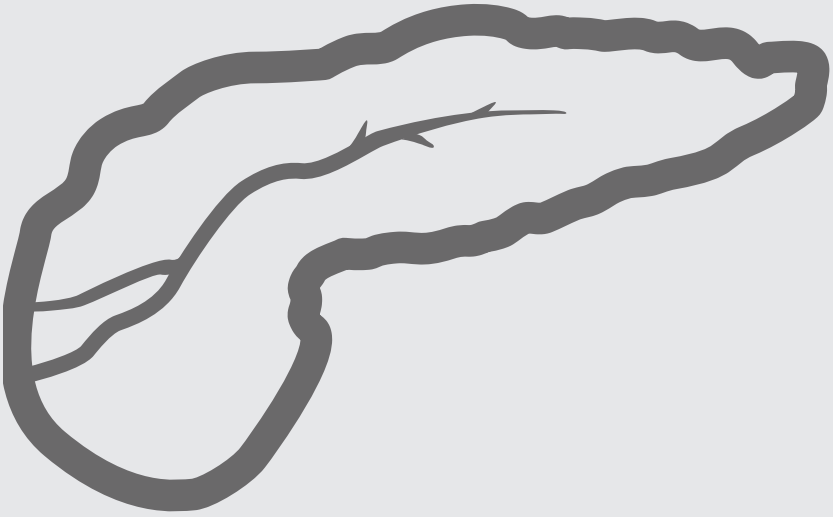
Curriculum Vitae



CURRICULUM VITAE

De auteur van dit proefschrift werd op 9 juni 1982 geboren te Groningen. In 2000 behaalde zij haar Gymnasium diploma aan het Willem de Zwijger college te Bussum. Hierna reisde zij voor een jaar af naar Barcelona om Spaanse Cultuur Wetenschappen aan de Universiteit van Barcelona te studeren, waar zij in 2001 haar propedeuse voor behaalde. In afwachting van de studie geneeskunde, waarvoor zij één keer werd uitgeloot, behaalde zij in 2002 haar propedeuse voor Nederlands recht aan de Vrije Universiteit te Amsterdam. In 2002 startte zij met de studie Geneeskunde aan de Vrije Universiteit van Amsterdam, waarvoor zij in 2007 haar doctoraal behaalde. In 2008 doorliep zij haar coschap heelkunde in het St. Maarten Medical Center, St Maarten, Nederlandse Antillen en haar keuze coschap Hepatologie aan het Queen Elizabeth Hospital te Birmingham, UK. Haar oudste coschap deed zij vervolgens op de afdeling Maag-, Darm-, en Leverziekten van het Medisch Centrum Alkmaar, waarna zij in 2009 haar artsexamen behaalde. In mei 2009 startte zij met promotieonderzoek naar 'de klinische aspecten en behandeling van exocriene pancreasinsufficiëntie bij chronische pancreatitis en pancreascarcinoom' op de afdeling Maag-, Darm-, en Leverziekten van het Erasmus Medisch Centrum te Rotterdam onder begeleiding van prof. dr. M.J. Bruno en dr. D.L. Cahen. Per 1 mei 2013 is zij met veel plezier gestart met haar opleiding tot Maag-, Darm-, en Leverarts aan het Leids Universitair Medisch Centrum (opleider: dr. R.A. Veenendaal). De vooropleiding Interne Geneeskunde volgt zij gedurende 2 jaar in het Sint Lucas Andreas Ziekenhuis te Amsterdam (opleider: dr. C.E.H. Siegert).

PhD Portfolio



PhD PORTFOLIO

Oral presentations

2012 Prospective evaluation of the prevalence of fat-soluble vitamin deficiencies and decreased bone mineral density in chronic pancreatitis
Dutch Society of Gastroenterology, the Netherlands

2012 Prospective evaluation of the incidence and prevalence of exocrine insufficiency in patients with irresectable pancreatic adenocarcinoma
Dutch Society of Gastroenterology, the Netherlands

2011 Practice of pancreatic enzyme replacement therapy in patients with exocrine insufficiency; a northern European survey
European Pancreatic Club, Magdeburg, Germany

2010 An update on pancreatic enzyme replacement therapy
United European Gastroenterology Week, Barcelona, Spain

2010 Prescription and response to pancreatic enzyme therapy in exocrine insufficiency due to chronic pancreatitis; a Dutch national survey
Dutch Society of Gastroenterology, the Netherlands

Poster presentations

2013 A prospective assessment of the influence of pancreatic cancer resection on exocrine pancreatic function
Digestive Diseases Week, Orlando, United States

2012 A prospective assessment of the natural course of the exocrine pancreatic function in patients with a pancreatic head tumour
United European Gastroenterology Week, Amsterdam, the Netherlands

2012 Prospective evaluation of the prevalence of fat-soluble vitamin deficiencies and decreased bone mineral density in chronic pancreatitis
Digestive Diseases Week, San Diego, United States

2011 Practice of pancreatic enzyme replacement therapy in patients with exocrine insufficiency; a northern European
Digestive Diseases Week, Chicago, United States

2010 Prescription and response to pancreatic enzyme therapy in exocrine insufficiency due to chronic pancreatitis; a Dutch national survey
Nominated as 'poster of distinction'
United European Gastroenterology Week, Barcelona, Spain

2010 Prescription and response to pancreatic enzyme therapy in exocrine insufficiency due to chronic pancreatitis; a Dutch national survey
Nominated as 'poster of distinction'
Digestive Diseases Week, New Orleans, United States

2010 Does consultation of a dietician in patients with chronic pancreatitis and exocrine insufficiency make a difference? A Dutch national survey
Digestive Diseases Week, New Orleans, United States

Statistical training

2012 English Biomedical Writing
Erasmus University Medical Center, Rotterdam, the Netherlands

2010 Young Investigator Workshop
United European Gastroenterology Week, Barcelona, Spain

2009 Principles of research in Medicine
NIHES, Erasmus University Medical Center, Rotterdam, the Netherlands

2009 Introduction to Data-analysis
NIHES, Erasmus University Medical Center, Rotterdam, the Netherlands

2009 Medical Statistics for Gastroenterologists
Amsterdam, the Netherlands

Memberships

2009 Dutch Society of Gastroenterology