Chronic pancreatitis
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CHAPTER 1
GENERAL INTRODUCTION AND OUTLINE OF THESIS

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BACKGROUND

Chronic pancreatitis (CP) is an inflammatory disease of the pancreas. The most prominent symptom is abdominal pain, which often leads to recurrent hospitalizations, absence of work, multiple interventions, and opioid addiction. The pain in CP is intense, recurrent and long lasting, with a major impact on the quality of life and social functioning of patients [1;2]. Ten years after onset of the disease, more than half of the patients are still suffering from pain [3]. The ongoing inflammation often leads to fibrosis and pancreatic function loss. Within 5 years, 50% of the patients becomes endocrine insufficient and 80% exocrine insufficient [4;5]. CP patients have a 3.6-fold increased mortality rate, compared with the general population [6].

Pathophysiology

The most frequent cause of CP is alcohol toxicity. In addition, a genetic predisposition, use of certain types of medication, anatomic abnormalities, and autoimmunity can play a role [7]. The pathogenesis of pain in CP is incompletely understood and is likely multifactorial. In patients with an outflow obstruction of the pancreatic duct (PD) due to strictures, calculi or both, it is hypothesised that pain arises from increased ductal and parenchymal pressure [8-11]. The observation that endoscopic or surgical treatment of the PD obstruction relieves pain supports this hypothesis [12;13]. In addition, several other causes of pain have been suggested, such as ongoing inflammation, local complications (e.g., bile duct and duodenal stenosis), and alterations in pancreatic nerves, including an increase in nerve fibers and neurogenic inflammation [14-16].

Diagnosis

The diagnosis is often made by a combination of clinical symptoms (e.g., abdominal pain, malabsorption, diabetes mellitus), pancreatic function tests (e.g., faecal elastase-1), and morphological abnormalities seen on imaging (e.g., calcifications, ductal lesions, pseudocysts) [17;18]. Imaging plays a key role in the diagnosis and therapeutic management of patients with CP. The most frequently used imaging modalities for CP are endoscopic ultrasonography (EUS), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance imaging (MRI), computed tomography (CT), and ultrasonography (US). Several diagnostic tools are used in practice, such as the Mannheim, Lüneburg, and Büchler diagnostic tools [17-19].

Treatment

Adequate treatment of pain in CP remains a major challenge, because evidence based treatment protocols are lacking. Treatment of pain in CP consists of medical, endoscopic, and surgical therapy. While some patients can be managed conservatively, endoscopic and surgical procedures are inevitable in cases with intractable pain and specific morphological abnormalities. To select the optimal treatment for the individual CP patient, one should consider the presence of ductal dilatation, the localization of the disease (i.e. head or tail), the presence of an enlarged pancreatic head, and other local complications (e.g., common bile duct stenosis, splenic vein thrombosis, portal hypertension, duodenal stenosis, pseudocysts).

Endoscopic treatment

The aim of endoscopic therapy in patients with CP is to provide adequate drainage of the PD by decompression of the duct and restoring outflow of pancreatic juice. This may lower intraductal pressure and thereby reduce pain. This can be achieved by means of extracorporeal shock...
wave lithotripsy (ESWL) or endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and stone extraction and/or dilatation of PD strictures and temporarily stent insertion.

**Surgical treatment**
The primary goal of surgery is long-term pain relief and control of the complications associated with CP. The optimal surgical procedure should manage the pain, preserve a maximum of endocrine and exocrine function still present, resolve complications of adjacent structures whenever possible (e.g., duodenal stenosis), reduce or free of opioid use and restore quality of life. Several surgical strategies are available for the treatment of pain in CP, and can be categorized into three major groups of procedures: drainage procedures, procedures combining drainage and resection, and resectional procedures. One of these strategies is chosen based on the presence of morphological features of the pancreas (e.g., inflammatory mass of head or tail, strictures/dilatation of the PD, duct disruption) and involvement of adjacent structures (e.g., duodenal or CBD stenosis, portal hypertension with newly formed vascular collaterals).

**Endoscopic versus surgical treatment**
Thus far two randomized trials have compared endoscopy with surgery in patients with CP [12;13]. Endoscopic drainage seems inferior to surgery in symptomatic patients with advanced CP. The question is if this is also true for patients in an early phase of the disease. Longitudinal studies show that of all CP patients, 40 to 75% will require surgery in the course of the disease [1;4;20]. Progression to severe and intractable pain is considered necessary, before invasive treatment is considered [21]. This approach can be questioned, because evidence suggests that early intervention can mitigate the disease progression, achieve pain control, and preserve the pancreatic function. The timing of surgery remains an important dilemma, as conclusive evidence is lacking [22-24].
OUTLINE OF THE THESIS

This thesis is divided in three parts. The first part focuses on the diagnostics in CP. The second part explores the natural course of CP. The third part evaluates the treatment of CP.

PART I - DIAGNOSTICS IN CHRONIC PANCREATITIS

There is lack of international consensus regarding the initial diagnosis of CP, particularly at its early stages. The diagnosis is often made by a combination of clinical symptoms (e.g., abdominal pain, malabsorption, diabetes mellitus), pancreatic function tests (e.g., faecal elastase-1), and morphological abnormalities seen on imaging (e.g., calcifications, ductal lesions, pseudocysts) [17;18]. Imaging is an indispensable and crucial part of the diagnostic and therapeutic evaluation of patients with chronic pancreatitis (CP). In Chapter 2 we summarized the data in a meta-analysis to determine the diagnostic accuracy of imaging modalities for the initial diagnostic assessment of CP.

International guidelines advise to perform primary imaging using the least invasive and widely available methods such as computed tomography (CT) or magnetic resonance imaging / cholangiopancreatography (MRI/MRCP) [21;25-28]. The choice of imaging modality could potentially have important consequences for diagnosis and treatment of patients with CP. The presence of intraductal stones, calcifications, or pseudocysts may dictate management strategies. Hence, a good understanding of the differences, strengths, and limitations of CT and MRI can improve individual clinical-decision making in patients with CP. Despite the abundance of reports in literature on the use of CT and MRI for CP assessment, a comparative analysis between these two modalities is still lacking. In Chapter 3, we compared CT with MRI in patients with CP to evaluate differences in characterization of type and extent of CP and interobserver agreement.

An accurate diagnostic tool is important for the diagnosis, treatment and follow-up of patients with (suspected) CP. This could lower the burden of additional diagnostic examinations, unnecessary resource utilisation and allow for timely treatment [25;26]. There is, however, much controversy about the diagnosis of CP. Several diagnostic tools have been proposed, which are used in the daily practice and for research purposes, such as the Mannheim, Lüneburg, and Büchler diagnostic tools [17-19]. These diagnostic tools, however, have marked differences in the individual diagnostic criteria they are composed of (i.e. clinical, morphological and functional criteria). In Chapter 4 we evaluated and compared three widely used diagnostic tools for CP, i.e. Mannheim, Büchler and Lüneburg diagnostic tools.

PART II - NATURAL COURSE OF CHRONIC PANCREATITIS

Few long-term prospective cohort studies have been performed to study the natural course, diagnosis and outcome of treatments [4;29-31]. The Dutch Pancreatitis Study Group (DPSG) has been successful in conducting several multicenter research projects facilitated by the advantageous geographic and demographics properties of the Netherlands [32;33]. It is estimated that in the Netherlands there are approximately 300 to 800 new cases of CP every year [34;35]. With coverage of over 30 out of 100 hospitals in the Netherlands, including all eight Academic Centers, the DPSG has the potential of including large numbers of patients in a relatively short time. The Dutch Chronic Pancreatitis Registry (CARE), outlined in Chapter 5, has been designed to utilize this potential to prospectively evaluate and follow-up patients with CP on a national level.
In Chapter 6 we conducted a study to describe the long-term outcomes in terms of recurrent pancreatitis and progression to CP in a large cohort of patients with a first acute pancreatitis episode collected during a previous randomized trial [32]. Although most patients with acute pancreatitis recover completely, a small group may develop recurrent pancreatitis or progress to CP [36;37]. Studying these aspects may offer ways for an earlier diagnosis and a better understanding of the underlying pathophysiology. This in turn may help to identify strategies for preventing disease progression.

PART III - TREATMENT OF CHRONIC PANCREATITIS

Many patients with CP undergo a surgical intervention for pain in the course of their disease, because medical and endoscopic therapy often fail to alleviate pain symptoms for a long period of time [4;31]. However, many patients are not suitable candidates for these interventions, since they lack an inflammatory mass or dilated pancreatic duct that could be treated surgically. Thoracoscopic splanchnicectomy can be a potential treatment for pain in CP [38]. However, several studies have been published, which show good short-term pain relief, but worsened outcome over time [39;40]. Evidence has emerged that prolonged use of opioids may result in sensitization of peripheral nerves, leading to a permanent hyperalgesic state, that is very difficult to manage and reverse [41-43]. This may explain the limited use of thoracoscopic splanchnicectomy. In Chapter 7 we performed a systematic review to evaluate the role of preoperative opioid use on the success of thoracoscopic splanchnicectomy in terms of long-term pain relief.

There is little insight into what drives the decision making of surgeons and gastroenterologist in the various aspects of the diagnostic workup and treatment of CP. The aim of Chapter 8 was a multidisciplinary international study to gain more insight into the current opinion and clinical decision making of international pancreatologists and to systematically identify key study questions regarding the diagnosis and treatment of CP for future research.

At present, conservative management is always the first step, even in patients with clear morphological changes. The timing of surgery remains an important dilemma, as conclusive evidence is lacking [22-24]. In Chapter 9 a randomized controlled multicenter trial is described, which evaluates the benefits, risks and costs of early surgical intervention: the Early Surgery versus Optimal Current Step-up Practice for Chronic Pancreatitis (ESCAPE) – trial.
REFERENCES

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