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Diagnosis and management of chronic pancreatitis: current knowledge

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Summary

This paper reviews the current literature on chronic pancreatitis (CP). Despite marked progress in diagnostic tools, predominately imaging methods, no consensus has been reached on the nomenclature of CP, ie diagnosis, classification, staging, pathomechanisms of pain and its optimal treatment. A major problem is that no single reliable diagnostic test exists for early-stage CP except histopathology (rarely available). This stage is characterised typically by recurrent acute pancreatitis ± necrosis (eg pseudocysts). Acute pancreatitis is a well-defined condition caused in 80% of cases by gallstones or alcohol abuse. Alcoholic pancreatitis, in contrast to biliary pancreatitis, progresses to CP in the majority of patients. However, a definite CP-diagnosis is often delayed because progressive dysfunction and/or calcification, the clinical markers of CP, develop on average 5 years from disease onset. The progression rate is variable and depends on several factors eg aetiology, smoking, continued alcohol abuse. Repeated function testing eg by the faecal elastase test, is the best alternative for histology to monitor progression (or non-progression) of suspected (probable) to definite CP. The pathomechanism of pain in CP is multifactorial and data from different series are hardly comparable mainly because insufficient data of the various variables ie diagnosis, classification, staging of CP, pain pattern and presumptive pain cause, are provided. Pain in CP is rarely intractable except in the presence of cancer, opiate addiction or extra-pancreatic pain causes. Local complications like pseudocysts or obstructive cholestasis are the most common causes of severe persistent pain which can be relieved promptly by an appropriate drainage procedure. Notably, partial to complete pain relief is a common feature in 50–80% of patients with late-stage CP irrespective of surgery and about 50% of CP-patients never need surgery (or endoscopic intervention). The spontaneous "burn-out" thesis of CP is in accordance with this observation although precise data of this phenomenon are scarce. Recent observations indicate that the progression to late-stage CP is markedly delayed in non-alcoholic compared to alcoholic CP. Therefore, spontaneous pain relief is also delayed but it occurs in close association with severe exocrine insufficiency suggesting that aetiology has a major impact on the duration of early-stage CP and that the "burn-out" thesis appears valid both in uncomplicated alcoholic and non-alcoholic late-stage CP. For treatment of steatorrhea and diabetes the reader is referred to recent reviews. Mortality and survival are closely related to aetiology with an increased death rate of about 50% within 20 years from onset in alcoholic CP compared to a markedly better prognosis in hereditary and idiopathic "juvenile" CP. The risk of pancreatic cancer is increased particularly in non-alcoholic CP based on the longer survival, whereas the risk of extra-pancreatic (smoking-related) cancer is about 12-fold higher in alcoholic CP.

Key words: chronic pancreatitis; alcohol abuse; pancreatic cirrhosis

Introduction

Chronic pancreatitis (CP) is a progressive inflammatory process of the pancreas leading eventually over several years to pancreatic "cirrhosis" [1–3]. Clinically, CP is usually characterised by an initial stage of recurrent acute pancreatitis (early-stage CP) and progressive pancreatic dysfunction and/or calcification (late-stage CP). Alcohol abuse is the prominent risk factor of CP (70%), while CP remains aetiologically undetermined in about 25% or is related to rare causes such as genetic mutations, hyperparathyroidism, trauma or "autoimmunity" [3, 4]. The main purpose of this review is a critical discussion of some controversial issues on diagnosis and treatment of CP based on the current literature and the personal long-term experience with CP.

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Are function tests obsolete for the diagnosis of CP?

Up to the late sixties pancreatic function tests, particularly the secretin test (ST) or the pancreozymin-secretin test (PST), in combination with pancreatic calcification were the diagnostic golden standards of CP in clinical practice. The diagnostic value of the various function tests (intubation vs tubeless tests) has been reviewed recently [5–7]. Accordingly, the "invasive" tests (ST or PST) are still the golden standard of function testing but the application of these tests has declined in the past 30 years from 50 to 10% [5, 7], primarily because the tests are laborious and costly. Preliminary studies collecting pancreatic juice endoscopically after short-term hormonal stimulation show an insufficient sensitivity [8].

Sensitivity of the "tubeless" tests ie faecal chymotrypsin, PABA-, Pancreolauryl- and faecal elastase test is insufficient for detecting minor or moderate insufficiency; approximately 25 to 50% compared to the PST [5, 6] or the grade of ductal alterations by ERCP [9]. Moreover, the tubeless tests except for the recently introduced faecal elastase test are commercially not available in the USA [6]. Thus, the general opinion prevails that function tests are of limited diagnostic value, particularly in early-stage CP [3]. Function testing is, however, indispensable for monitoring progression to late-stage CP and for detecting the diminished pancreatic secretory capacity observed in late-stage CP, which is typically associated with spontaneous pain relief (see below).

Diagnostic value of imaging methods in CP?

With the advent of numerous new morphological methods in the past 30 years ie ERCP, ultrasound, computer tomography, endoscopic ultrasound, magnetic resonance (MR) and positron emission tomography (PET), the imaging methods gained increasing importance in the diagnosis of pancreatitis. The elucidation of pancreatic pathology is particularly helpful in the diagnosis of and staging acute pancreatitis ie detection of severe necrotising forms. Evidently, late-stage CP can be diagnosed reliably by most of the imaging methods, for instances MR instead of ERCP but also by routine ultrasound eg "large-duct CP" or plain abdominal x-ray for calcific CP. The diagnostic accuracy of the new imaging methods in early-stage CP is not precisely defined and additional studies are required for the validation of these methods compared with the golden standard of early-stage CP ie histopathology [3]. The lack of a routine method comparable to liver biopsy remains the major challenge for such an analysis. Thus, no single imaging test has been validated adequately for diagnosing early-stage CP [3].

The relationship between acute and chronic pancreatitis

The controversy regarding the classification of CP was based on the disputable relationship between acute pancreatitis and CP. The Marseille-experts postulated in the early sixties that acute and CP are two separate nosological entities, which rarely merge. This thesis was primarily based on the observation that in a cohort of acute pancreatitis the mean age was 13 years higher than in the CP-series [10]. This difference was, however, due to the high percentage of gallstone pancreatitis in the Marseille series of acute pancreatitis (54%), which is known to virtually never progress to CP [11]. There is now increasing evidence that alcoholic acute and CP represent different stages of the same nosological entity ("necrosis-fibrosis" hypothesis) [2, 12]. This notion is supported by experience in hereditary CP [12].

Acute pancreatitis is a short event that is clinically, biochemically and morphologically well-defined. On the contrary, CP is a slow process evolving clinically in 2 stages, i) early-stage CP with recurrent clinical acute pancreatitis and ii) late-stage CP with exocrine insufficiency, diabetes and calcification [13]. In clinical practice, acute and late-stage CP are easily diagnosed. The key problem is the rather long interval that exists between onset and definite late-stage alcoholic CP (an average of 5 years) [3, 11, 13]. In other words, a diagnostic "window" or "black-box" typically exist between onset ie early-stage CP and the definite CP-diagnosis, except in patients with surgical biopsies (figure 1). The progression rate to late-stage CP is quite variable [14]. This seems to be related primarily to aetiology (see below) and to additional factors particularly smoking. Recent studies indicate that smoking markedly accelerated the progression to calcification and/or diabetes both in alcoholic CP [15] and in non-alcoholic (idiopathic) CP [16]. Moreover, alcohol abstinence may delay the progression to late-stage CP [17].

An additional unsettled key problem is to differentiate post-acute fibrosis (cicatrisation) and

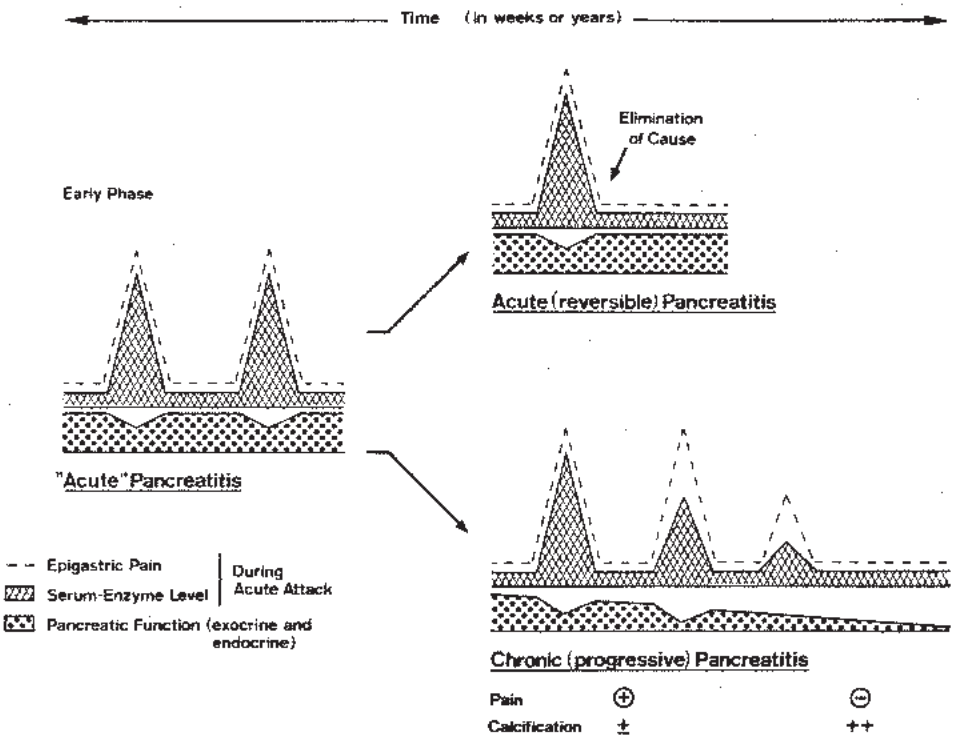


Figure 1

Scheme of classification of pancreatitis based on the pertinent clinical, functional and morphological features during long-term evolution from onset. The disease starts with typical episodes of acute (recurrent) pancreatitis irrespective of aetiology. Elimination of the causative factor, eg gallstones, is typically followed by a "restitutio ad integrum" of the pancreas with cessation of further pancreatitis, ie acute (reversible) pancreatitis. Contrariwise, chronic (progressive) pancreatitis caused eg by alcohol, heredity is characterised by progression to exocrine insufficiency, diabetes, pancreatic calcification, in 50–80% of patients in association with spontaneous pain relief (compatible with "burn-out" of CP).

progressive fibrosis as typically noted in CP [11]. Ductal stenosis/dilatation is observed for variable time following biliary acute pancreatitis. In a recent study, such ductal changes were observed (by MRCP) 5 years after recovery from acute biliary pancreatitis in over two thirds of 40 patients [18, 19]. Whether such ductal changes are due to post-acute scarring or evidence of an initial stage of CP is unsettled and requires further long-term studies. Such studies should include function testing to prove or disprove CP [19].

Notably, pancreatic ductal alterations are observed with increasing frequency in relation to aging [3, 20]. These observations indicate that pancreatic injuries of similar appearance may follow different clinical courses. Therefore, caution is indicated in the interpretation of data in CP-series in which ERCP-alterations are used as the only diagnostic golden standard of CP. The intensive search over the past decades for a single reliable diagnostic test of early-stage CP next to histopathology has failed. Due to the spotty nature of initial CP lesions [2, 3] there is a risk of sampling error and of missing small ductal cancer with secondary CP. Hence, it seems unlikely that an ultrasound-endoscopically guided biopsy method will become a routine procedure.

International meetings of CP-classification

Despite numerous international expert meetings in the past 40 years, no consensus on the classification of CP exists (see recent reviews; 3, 20). The lack of a generally accepted CP classification explains to a large extent why data in the literature on diagnosis and treatment of CP from different centres are hardly comparable, except data on patients with advanced late-stage CP. A common terminology of CP including aetiology (see below) and a staging system based on a combination of the pertinent clinical, functional and morphological features from onset to late-stage CP is badly needed [3]. In 1994 [20] and 1997 [11] clinically based terminologies of CP were proposed, but these proposals were not generally recognised [3]. The proposal of 1997 focused on the topic of alcoholic CP, but according to the experts the terminology can also be used mutatis mutandis for non-alcoholic CP [11].

The experts agreed that clinically two forms of CP should be distinguished, ie 1) probable CP and 2) definite CP. A similar subdivision has been proposed by the Japan Pancreas Society [3, 21].

A history of recurrent clinical acute pancreatitis is the prominent initial clinical feature, except in patients with primary painless CP (ppCP).

1) **Probable CP** is characterised by a typical history and one or more of the following criteria:
- mild ductal alterations (Cambridge criteria, 11)
- recurrent or persistent pseudocysts
- pathological Secretin-test

– endocrine insufficiency ie abnormal glucose-tolerance test

2) **Definite CP**

One or more of the following criteria in addition to the typical history (and aetiology)

– pancreatic calcification
– moderate or marked ductal alterations (Cambridge criteria, 11)
– marked exocrine insufficiency defined as steatorrhea (>7 g/24 h), normalised or markedly reduced by enzyme substitution
– typical histology of an adequate surgical specimen

These stringent criteria of CP are based primarily on the fact that acute (recurrent) pancreatitis and late-stage CP are clinically defined entities and that a follow-up of clinical, functional and structural features from disease onset is essential for classification and staging of CP [11]. A total of 343 patients with definite CP were included in our prospective study since 1963 [22]. A similar number of patients with probable CP were excluded because follow-up was insufficient (death or loss) and a definite CP remained unproven. Obviously, pooled data of probable and definite CP result in large impressive CP-series but such data cannot be generalised. Pancreatic calcifications are virtually pathognomonic of CP and occur in up to 90% of late-stage CP [23]. Interestingly, calcifications tend to decrease spontaneously in about one third of CP-patients with long-term follow-up despite progressive exocrine insufficiency [23]. Thus, ductal stones appear to be a consequence rather than a primary pathogenetic factor. The pathophysiology of stone formation and dissolution is poorly understood. The hypothesis that a reduction of lithostatin – an acinar secretory protein postulated to prevent precipitation of calcium salts – might be a relevant pathogenetic factor of CP [10] seems unlikely according to recent data [3, 24]. Several current paradigm shifts in our understanding of CP involve the role of ducts,lithostatin, trypsinogen activation in acinar cells, stellate cell activation and fibrosis, and genetics that have been reviewed recently [3]. These topics are part of ongoing research aiming to improve our knowledge on the pathophysiology of CP – an issue beyond the scope of this review. For the diagnosis of CP, function testing has been abandoned in many centres despite the fact that histopathology as golden standard is rarely available and the diagnostic impact of the new imaging techniques in early-stage CP remains to be defined (see above). In our experience, function tests are the best alternative for histopathology in monitoring the typical progressive evolution of CP. A significant correlation between fibrosis and exocrine insufficiency was found in a series of 73 alcoholic CP-patients in whom histology was assessed in comparison with the clinical and functional long-term course [2] (figure 2, 3). This correlation was especially obvious in 10 patients with 2 histologic examinations, one in early-stage (surgical specimens) and the second in late-stage CP (post-mortem specimen;

Figure 2

Evolution of histopathological changes in pancreatic specimens of alcoholic chronic pancreatitis (n = 73) in relation to years from onset ie fibrosis (FS, fibrosis score 0–12), calcification (%) and necrosis (%) (modified from ref. [2]). During the observation period (0 to >13 years from onset), an almost 2-fold increase of fibrosis and a 3-fold increase of calcification was observed. Necrosis diminished from initially 75% to <10% during follow-up (in accordance with the necrosis-fibrosis-hypothesis; ref. [2]).

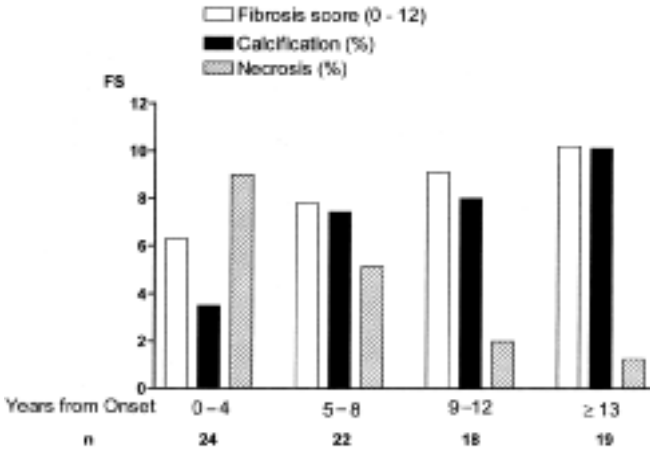
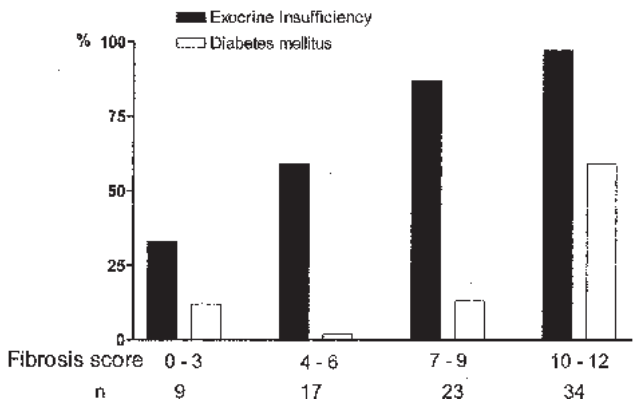


Figure 3

Evolution of progressive exocrine insufficiency and diabetes in relation to the fibrosis score (0–12) in the same series of alcoholic chronic pancreatitis (see fig. 2 and ref. [2]). A significant correlation is observed between fibrosis score (0–12) and exocrine insufficiency which indicates that function testing is the best surrogate of histology in documenting progression to late-stage chronic pancreatitis. Onset of diabetes is typically delayed in comparison with exocrine insufficiency in alcoholic chronic pancreatitis.



mean interval 8 years) [2]. Therefore, the surveillance of exocrine insufficiency eg faecal enzyme tests is pivotal in detecting progressive dysfunction as typically found in late-stage CP. The faecal chymotrypsin or elastase-1-test are more sensitive and specific than steatorrhea [3, 5–7, 25]. It may be argued that long-term surveillance by function tests delays the CP diagnosis which might be a disadvantage for the patient. However, "to falsely label a person as having CP based on questionable markers of early-stage CP is a significant concern. A misdiagnosis of CP is difficult to correct and may harm patients if potentially injurious treatments are undertaken eg endoscopic or surgical intervention" [9].

The pain profile and its relationship to structural and functional alterations during evolution from early- to late-stage CP

Pain is a prominent clinical feature of CP. Primary painless CP (ppCP) comprises a subgroup that manifests clinically with typical symptoms of late-stage CP and occurs rarely in alcoholic CP (<10%) but may be observed in about 50% of patients with idiopathic "senile" CP or in CP due to rare causes [14].

Different mechanisms of pain have been proposed [3, 13, 26–29]. The literature on this issue is abundant and controversial especially because the pathophysiology of pain is poorly understood. In most clinical series, the presumed pain cause is not stated. There is currently increasing evidence that pain in CP is multi-factorial (13, see reviews 26–31). Several aspects explain in part that no consensus on pain mechanisms and on the optimal pain management has been reached, namely:

1) Most interventional surgical or endoscopic series on pain mechanisms (and therapy) are biased because they are focused on CP-patients with severe pain and exclude approximately 50% of CP-patients who never needed a pain-relieving intervention [13].

2) The results of pain management from different centres and by different therapeutic modalities are hardly comparable mainly because no precise data on pain profile, classification + staging and the presumed pain cause are provided.

3) Pain in CP is variable ranging from mild to severe and from intermittent to persistent. No recognised pain score system exists. For instance, severe pain defined by the regular intake of opiates jeopardises the differentiation of CP-related pain and opiate addiction [13]. Moreover, "intractable pain" that is often used in the current literature rarely occurs in CP except in opiate addicts, in the presence of cancer or in patients with extra-pancreatic pain causes. In a recent study, two types of pain in CP were distinguished, *1) A-type pain*, characterised by episodes of acute pancreatitis, separated typically by long pain-free periods of months (or years). These episodes, usually lasting 2 to <10 days, may be severe with need of hospitalisation; *2) B-type pain* ie prolonged periods of either persistent (daily) and/or clusters of recurrent severe pain exacerbations for at least 2 months and requiring repeated hospitalisations and surgery in most instances [13].

Recurrent acute pancreatitis (morphologically acinar inflammation ± necrosis) is the prominent clinical feature of early-stage CP [1–4, 13, 20]. Persistent severe B-type pain was observed primarily in association with local complications ie pseudocysts (66%; typically in early-stage CP; 3.7 years from onset) or obstructive cholestasis (16%, typically in late-stage CP; 12 years from onset) [13]. The cause of these complications was reliably documented by imaging studies in combination with function tests and promptly relieved by an appropriate drainage procedure. Severe B-type pain presumably caused by ductal (tissue) hypertension occurred in less than 15% of patients, which suggests that this pain mechanism is often overestimated in the current literature [13].

Only 4 patients of our series (3%) were operated with a pancreatic head resection.

Thus, an inflammatory process in the pancreatic head associated with a "neuro-inflammatory reaction" necessitating pancreatic head resection for pain relief [25, 26] does not represent a major pain cause of CP in our experience [13]. Spontaneous partial or complete pain relief in late-stage CP is a common phenomenon noted in 50–80% of CP-patients with long-term follow-up irrespective of surgical or endoscopical interventions [1–3, 13, 20, 32–40].

These studies with spontaneous pain relief are difficult to compare since these are retrospective analyses, often with a mixture of alcoholic and non-alcoholic CP, variable follow-up and a lack of CP-staging. However, most experts agree that pain due to recurrent pancreatitis ± pseudocysts occurs predominately within the first 3 to 6 years from onset [32–39], and that pain disappears (or decreases) in relation to duration of CP from onset. For instance in the series of Ink (n = 77) pain relief increased from 17% to 62% from 2 to 8 years after onset [38] or in the series of Lankisch (n = 335 patients) 11% became pain-free within 5 years, 24% from 5 to 10 years and 65% after 10 years [36]. Scuro et al. (n = 191) noted pain relief after a mean follow-up of 10 years in 70% of surgical and in 54% of non-surgical patients [33] and according to the data of the Mayo-Clinic 70% of CP-patients of alcoholic and non-alcoholic CP became pain-free irrespective of surgery [37]. Surprisingly,

the phenomenon of spontaneous pain relief has not been analysed adequately except in few studies. In the experience of our group [13] and others [40], a close correlation between pain relief and severe exocrine insufficiency was documented – the so-called "burn-out" of CP first described >30 years ago [41]. This hypothesis is still debated in the context of the current controversy on pathomechanisms of pain in CP [26, 27, 30, 42, 43]. It seems likely that the delayed progression rate in non-alcoholic CP may explain at least in part the controversy (see below, impact of aetiology). A prospective multi-centre study of a mixed medical-surgical series on a larger scale is mandatory.

Unfortunately, the only large scale study of this type with two German centres had to be abandoned after 5 years in 1982 because of problems in maintaining the necessary collaboration between the 3 centres.

There are some exceptions to the "burn-out" thesis [13]. For instances, B-type pain may be observed in late-stage CP due to painful obstructive cholestasis, spontaneous pancreatic/hepatic abscesses [13, 44–46] or extra-pancreatic pain causes like opiate addiction, peptic ulcer, cancer [13]. Few patients with advanced CP continue to complain of persistent pain mainly because this is the only guarantee for continued support by social insurance – a problem that is difficult to investigate accurately except in patients with documented "burn-out" late-stage CP lacking evidence of local CP-complications, extra-pancreatic pain causes or opiate abuse [43]. The impact of continued alcohol abuse on the pain profile in CP is debated. Advanced alcoholic CP becomes "immune" toward alcohol [13, 47] and alcohol abuse, in contrast to opiate addiction, has no impact on the pain profile once the patients has reached advanced CP. Mortality and working incapacity are, however, three times higher in patients with continued alcohol intake [13]. On the other hand, alcohol abstinence in early-stage CP is the treatment of choice in preventing further episodes of pancreatitis [48]. Moreover, the progression rate of alcoholic CP is delayed by cessation of alcohol intake [17]. The surgical management of pain in CP has been reviewed recently [31] and does not need further discussion except for the controversy between surgical and endoscopic interventions [30]. In the last few years endoscopic interventions for pain relief based predominately on the "obstructive pain concept" have been propagated as alternative to surgery ie sphincterotomy, stent placement, endoscopic stone extraction ± lithotrypsy, cyst drainage [see 30, 49]. To our knowledge, only 1 prospective partly randomised study on this problem has recently been published [50]. The experts provided evidence that the initial success rate of pain relief within the first year was identical with both methods, but at 5 years follow-up pain relief was higher in the surgical series ie 37% compared to 14% in the endoscopic series. The very low rate of lasting pain relief by surgery compared to the current literature (70–85%; 31) is surprising. Notably, long-term studies on pain relief by surgery or endoscopy have to be interpreted with caution since spontaneous pain relief is known to occur with increasing frequency in relation with late-stage CP (see above; and figures 4/5). In summary, an improved knowledge of the pathomechanism(s) of pain and of the long-term pain profile in CP is fundamental for a rational therapeutic strategy. Further prospective studies of mixed medical (endoscopic) surgical series based on a standardised terminology (eg diagnostic criteria, staging, aetiology) are required as solid fundament for improving our knowledge of this clinically relevant problem.

Impact of aetiology on course and outcome of CP

CP can be classified aetiologically according to the TIGAR-O-system [3]:

T-oxic eg alcohol, drugs [51], renal failure, hypercalcaemia [3], post-actinic [52]

I-diopathic eg idiopathic "juvenile" CP [53], "senile" CP [37, 54, 55], tropical CP [56, 57]

G-enetic; autosomal dominant trypsinogen-gene mutation or mutations of modifier genes eg CFTR-, SPINK-1-genes [3]

A-utoimmune pancreatitis [3, 58]

R-ecurrent severe acute pancreatitis

O-bstructive pancreatitis

In industrialised countries, the prominent risk factors of CP are alcohol (~70%)undefined idiopathic (25%) or rare causes (5%). Of major importance is the recent discovery of trypsinogen gene mutations (PRSS-1) in hereditary CP [3, 59]. In addition, an increase in the frequency of mutations of the trypsin secretory inhibitor gene (SPINKI) and/ or of cystic fibrosis genes (CFTR) have been reported primarily in idiopathic CP, which seem to provide an increased susceptibility to pancreatitis in association with other (undefined) factors [3, 59]. The studies on molecular genetics open new perspectives in our understanding of the pathophysiology of pancreatitis and in an improved classification of CP that requires further investigations – a topic of ongoing research that is beyond the scope of this review – [see recent reviews 3, 9, 59, 60]. Notably, in contrast to acute pancreatitis that is caused in 60 to 80% either by gallstones or alcohol, biliary pancreatitis virtually never progresses to CP. On the other hand, the majority of alcoholic acute pancreatitis seems to progress to CP but a probably small (undefined) percentage of

Figure 4

Probability of no exocrine insufficiency in relation to years from disease onset of chronic pancreatitis of different aetiology (Kaplan-Meier). The progression to exocrine insufficiency was significantly delayed in hereditary (HP, n = 11) and idiopathic "juvenile" (IJCP, n = 26) compared to alcoholic (ACP, n = 265) and idiopathic "senile" (ISCP, n = 46) chronic pancreatitis (see ref. [22]).

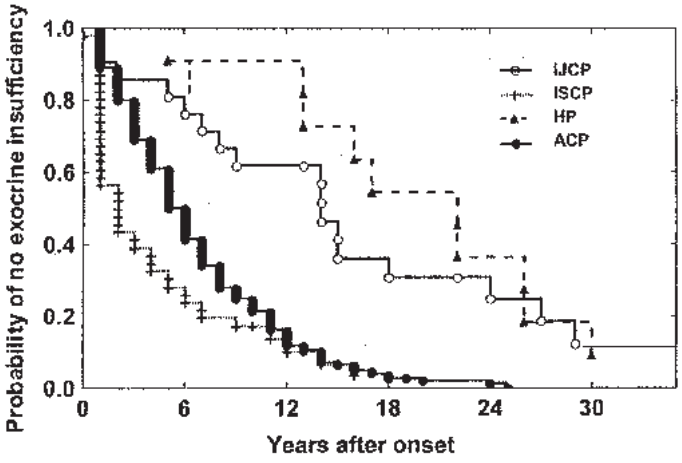
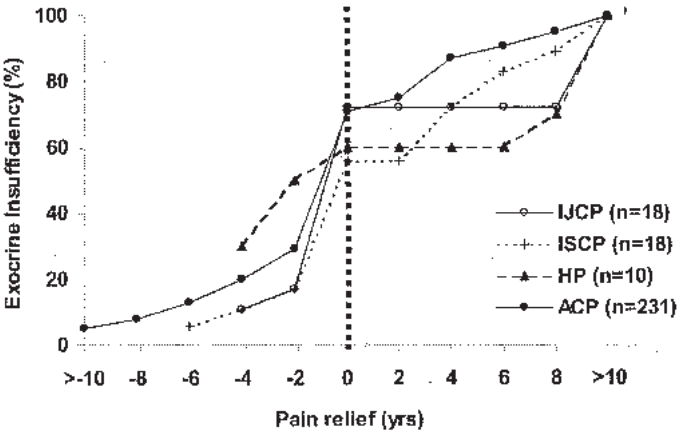


Figure 5

A close relationship between pain relief (>2 years) (Time 0) and exocrine insufficiency was observed in 60 to 80% of patients both in alcoholic (ACP, n = 231) and in non-alcoholic chronic pancreatitis ie hereditary (HP, n = 10) and idiopathic "juvenile" chronic pancreatitis (IJCP, n = 18). From this analysis patients with primary painless chronic pancreatitis were excluded (about 50% of cases with idiopathic "senile" chronic pancreatitis; <10% with ACP) or patients with opiate addiction (<5% with ACP) (see ref. [22]).

Note: despite the delayed progression to exocrine insufficiency in HP and IJCP (figure 4), a similar percentage of patients got pain relief in close association with exocrine insufficiency regardless of aetiology (and surgery) suggesting that the "burn-out" thesis appears valid both for alcoholic and non-alcoholic (uncomplicated) chronic pancreatitis (see text).



these patients do not progress [11, 61, 62]. The lack of a reliable animal model of CP hinders the scientific progress on this issue. Moreover, only <10% of chronic alcoholics develop pancreatitis which indicates that additional, still undefined factors eg genetic, environmental or nutritional are responsible for inducing CP [3]. Data on the impact of aetiology on the evolution of CP are scarce and controversial except for alcoholic CP. The author of a recent review postulated that aetiology has no impact on course and outcome of CP [42]. This thesis is in accordance with the clinical experience that there is a common final pathological pathway to late-stage CP ie "cirrhosis", irrespective of aetiology [3] with only few exceptions eg "autoimmune" pancreatitis that can be treated successfully with steroids [58] or "obstructive" pancreatitis that recovers following elimination of the obstruction [3].

In contrast to this view, our groups and others presented evidence that the progression rate to late-stage CP differs markedly in relation to aetiology as documented by a significant prolongation of the precalcific (painful) early-stage and a marked delay in onset of calcification and exocrine insufficiency in hereditary and idiopathic "juvenile" CP compared to alcoholic CP [22, 37, 55, 63–65] (figure 4). The link is less well evident in idiopathic "senile" CP since about 50% of these patients have primary painless CP; undefined onset of CP and steatorrhea or diabetes are the most predominant initial symptoms of this entity [22]. Thus, aetiology is a relevant variable of the progression rate of CP which is usually neglected in the current literature on diagnosis and therapy of CP. For instance, the observation that a large percentage of CP sufferers have recurrent pain for >10 years from onset [42] contrasts with our experience in alcoholic CP [13]. This may, at least in part, be due to the inclusion of 25 to 40% of patients with non-alcoholic CP in the series cited by Lankisch [42]. Interestingly, permanent pain relief was observed in 60 to 80% in association with calcification and severe exocrine insufficiency in the non-alcoholic CP-series, which is supporting the "burn-out" thesis regardless of the delayed progression rate compared to alcoholic CP [22]. These observations emphasise that aetiology and staging based on exocrine function testing (in contrast to duration of CP from onset [42]) are major variables in predicting pain relief of uncomplicated CP regardless of surgical and/or endoscopic interventions [22] (figure 5). For secondary treatment options such as treatment of diabetes and/or steatorrhea, the reader is referred to excellent reviews on these topics [66, 67].

Mortality is markedly increased in alcoholic CP compared to the normal population amounting to approximately 50% at 20 years from onset, but the cause of death is directly related to CP in less than 20% [13, 37, 64, 68–70]. Mortality is significantly lower in hereditary and idiopathic "juvenile" CP [22, 37, 64, 68–70]. Hereditary CP carries a high cumulative risk of pancreatic cancer ie between 8.6% and 29% at 70 years of age [65] and an increased risk was also demonstrated in alcoholic CP [71, 72]. However, in this group of patients, the incidence of extra-pancreatic primarily smoking-related cancers is about 12 fold higher [13, 22, 64, 72, 73].

This review emphasises that the knowledge of the natural history is the "backbone" of diagnosis and management of CP, especially because early-stage CP cannot be diagnosed precisely at present without a surgical biopsy (rarely available). Of special importance is the exact analysis of the patient's and the disease characteristics eg pain profile, cause of A- and B-type pain, structural and functional alterations during the long-term evolution from disease onset. Based on the current experience, some of the discussed features such as aetiology and staging may help to predict in a given patient what is the risk for having a good or bad outcome without or with a surgical (or endoscopic) intervention.

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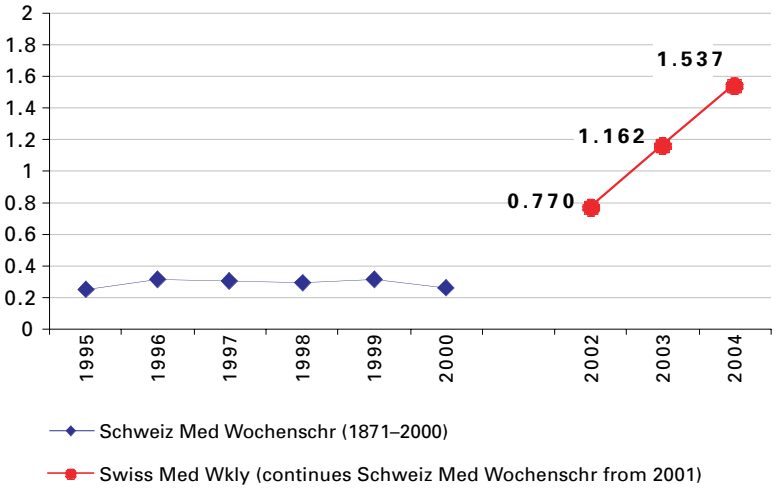

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