

# Endocrine Pancreatic Insufficiency in Chronic Pancreatitis

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## Key Words

Chronic pancreatitis · Endocrine pancreas · Pancreatic diabetes · Insulin · Glucagon · Elective pancreatic surgery

## Abstract

Chronic pancreatitis (CP) is considered to be a rare cause of diabetes mellitus. However, in both the developed and developing world, there is an increasing number of patients suffering from pancreatitis probably due to life-style changes, which is partially associated with both social factors and the poor health status of immigrants. Owing to these circumstances, CP has evolved with one of the possible causes of diabetes in a selected group of patients and should be included in the differential diagnosis of diabetes. Several studies have shown that the long-term rate of diabetic complications in patients with CP and insulin-dependent diabetes is similar to that in patients with type 1 diabetes of equal duration. The hypothesis that early diagnosis of CP should result in better prognosis is not validated and may complicate the issue, since the risk of diabetes has been shown to increase significantly only once pancreatic calcification has developed. Accumulative evidence suggests that the risk of diabetes is not influenced by elective pancreatic surgical procedures other than distal pancreatectomy. The lack

of contemporary data points to the urgent need for large prospective studies in order to accurately evaluate the special characteristics of disorders in glucose homeostasis in patients with CP.

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## Introduction

The pancreas is a major endocrine gland since its role in the tight regulation of glucose is vital for the human organism. Among the main hormones secreted from the pancreas are insulin, glucagon, pancreatic polypeptide (PP) and somatostatin. Under normal circumstances, a remarkably constant molar ratio exists between the serum levels of C-peptide, insulin, glucagon and PP [1]. In addition, in normal or pathological states, other peptides, such as vasoactive intestinal peptide, thyrotropin-releasing hormone, cholecystokinin (CCK), galanin, gonadotropin-releasing hormone, growth hormone [2–4] and the recently identified ghrelin [5] are also secreted, though their precise role in pancreatic physiology remains unclear. In animals, there is evidence of a close correlation between the pancreas and other endocrine organs, and this interaction depends on various neuropeptides (e.g. corticotropin-releasing factor) [6].

There are many lines of data in the literature studying the exocrine pancreatic secretion in patients with chronic pancreatitis (CP). Measurements of basal serum trypsinogen, fecal fat excretion, fecal chymotrypsin, fecal elastase concentration, and direct hormonal stimulation tests using duodenal tubes (secretin or secretin-CCK tests) have been performed in order to evaluate the exocrine pancreatic secretory capacity [7–12].

The incidence of (CP) appears to be in the range of 3–10 per 100,000 population in many parts of the world [8]. However, because of the different diagnostic criteria and methods used in the entity of CP, the real prevalence of CP in the western world could have been underestimated by far. In 1978, in a study based on hospital autopsy material, Olsen [13] found a combination of both fibrosis and chronic inflammatory cell infiltration in 52 of 394 histological sections (13%). Of interest, only 2 of these patients had a clinical diagnosis of (CP). Recently, Rothenbacher et al. [14] investigated the prevalence and main determinants of exocrine pancreatic insufficiency in a large population-based sample of older adults (525 women and 389 men, mean age 61.9 years), by measuring fecal pancreatic elastase-1 concentrations. 11.5% of the investigated subjects showed signs of an exocrine pancreatic insufficiency. Taken together, these findings suggest that the prevalence of CP may be much higher in the general population than previously estimated and consequently, a high number of patients with pancreatic diabetes should be expected.

In Western countries, alcohol is the cause of 70–90% of all cases of CP [10, 15]. The Scandinavian prospective study published in 1981, which was limited to alcoholic CP, noted an incidence of 8.2 cases per year per 100,000 population, and an overall prevalence of 27.4 cases per 100,000 population [11]. However, differences in alcohol consumption in different populations along with different diagnostic approaches and different diagnostic criteria reflect geographic variations in the incidence rates of alcohol-induced CP [16].

Tropical pancreatitis, on the other hand, is the most common form in certain areas, including Africa, Southeast Asia and India, where it is considered a disease of youth and early adulthood (over 90% of patients develop the illness prior to the age of 40 years) [17]. In an endemic area the reported prevalence of tropical pancreatitis reached approximately 0.12% with a mean age of onset of 24 years [18].

Other causes of CP, such as biliary, chronic hypocalcemia syndromes, hereditary pancreatitis and autoimmune are rare, while a significant percentage of patients

with CP (10–30%) present without a recognizable cause and are therefore assigned the idiopathic form [19]. The natural history of the disease varies considerably and may differ among the various etiologies [9, 16, 20].

Hereditary pancreatitis is the cause of less than 1% of CP. About 30% of the cases do not have a known cause and are defined as idiopathic. Cystic fibrosis is the most frequent recessive autosomal genetic disease found in Caucasians. Growing evidence suggests that environmental and possibly genetic cofactors must also be present before the mechanisms protecting the pancreas from pancreatitis are circumvented and pancreatitis develops [21]. In recent years several genes have been identified as being involved in disease onset: the cationic trypsinogen gene, responsible for some cases of hereditary pancreatitis [22], the cystic fibrosis transmembrane conductance regulator [23] and pancreatic secretory trypsin inhibitor [23, 24] genes, involved in sporadic idiopathic CP. Interestingly, mutations of cystic fibrosis transmembrane conductance regulator and pancreatic secretory trypsin inhibitor genes are present in about 40% of the idiopathic CP [22].

### **Progression of Exocrine and Endocrine Dysfunction after Acute Pancreatitis**

It remains uncertain whether the pancreatic function is diminished after acute pancreatitis (AP) and if there is an association between the severity of such an episode and the impairment of both exocrine and endocrine function. It is logical to assume that etiology could also play an important role in altering pancreatic function, with differences between the AP episodes of alcoholic and biliary origin.

Pareja et al. [25] examined prospectively the exocrine function of 63 cholecystectomized patients with acute biliary pancreatitis and reported no observable functional change a year later, regardless of the severity of the attack. Changes in hydrocarbonate metabolism described in AP are characterized by the presence of hyperglycemia and changes in insulin and glucagon secretion in up to 50% of the cases [26, 27] after an acute episode. Although there are poor data concerning the endocrine function, biliary pancreatitis seems to have fewer adverse long-term effects on the endocrine pancreas [25].

Normal response to glucose has been reported after recovery from an attack of acute alcohol-induced pancreatitis, and is often linked with increased insulin secretion, compared to normal subjects [28]. Regarding alcohol-induced CP (ACP), a long-term clinicomorphological study

was conducted concerning 73 patients who were followed up for a mean of 12 years and for whom either surgical or postmortem specimens of the pancreas were available [12]. Results showed a marked progression of fibrosis with duration of the disease, which was associated with an increased incidence of calcification and correlated with failure of exocrine and endocrine pancreatic function [12]. In contrast, Boreham and Ammori [29], in a small number of patients with acute episodes (7 severe, 16 mild) reported no correlation between functional recovery and the cause of the disease. According to their findings, exocrine insufficiency was associated with the severity of the attacks as well as with endocrine insufficiency.

A dynamic progression of alcoholic pancreatitis from early to late stages has been suggested, assuming that ACP represents the end stage of damage that has accumulated during multiple relapses of AP. Investigators have shown that some patients with relapsing alcoholic pancreatitis do not progress clinically to CP. However, progression of AP to ACP occurs in approximately 1 in 10 patients. This discrepancy is probably due to the variations in the extent of the damage after an acute episode, the localization of the injury (in and around the pancreas), and its consequences for the pancreatic duct system [30]. The incidence of both exocrine and endocrine insufficiency rises over time. Overt diabetes was observed in about 20% of patients with alcoholic CP at 6 years and in nearly 50% at 10 years from onset, while exocrine insufficiency occurred in approximately 55 and 80% of patients, respectively [31].

### Endocrine Function in CP

It has been suggested that CP may be associated with disturbed endocrine secretory capacity of the organ [1]. Thirty-five years ago, Bank et al. [32] divided their patients with CP into two subgroups. One group consisted of patients with impaired glucose tolerance (IGT) and the other group patients with normal glucose tolerance. In these two groups the arginine infusion test was performed in order to evaluate the insulin reservoir. Both groups of patients showed an impaired response to arginine and, moreover, the curve of insulin secretion in patients with abnormal glucose tolerance was 'flat'. In the same study, abnormal glucose tolerance due to attenuated insulin secretion was evident in 70–90% [32]. Cavallini et al. [33] suggested that glucose metabolism abnormalities in CP occur as a result not merely of impaired insulin produc-

tion but also as a result of the coexisting insulin resistance. Nevertheless, the particular cause of insulin resistance is still questionable. Patients with normal glucose tolerance test initially released insulin at a rate similar to that in healthy controls after glucagon test (C-peptide at 5 min), although at later times the secretory response was reduced. This functional exhaustion of the endocrine pancreas could be revealed only after the maximal stimulation with glucagon, whereas submaximal stimulation with oral glucose tolerance test failed to uncover the impaired insulin reserve. In patients with IGT, insulin response was markedly reduced, although insulin sensitivity (assessed by the K-ITT) was similar in the two groups, suggesting that the  $\beta$ -cell secretory deficit is the principal factor responsible for the glucose intolerance [33].

In addition, a low level of linoleic acid could be implicated in the insulin-resistance phenomenon [34]. This observation is of great interest, since decreased concentrations of linoleic acid have been reported in patients with CP, independent of the presence of diabetes [35].

On the other hand, the  $\alpha$  cells seem to be more resistant to the effects of CP. It has been reported that basal levels of glucagon are maintained in patients with CP, although the stimulated response is lowered [36, 37]. A recent study in 33 patients with CP and no obvious signs of cirrhosis reported that even basal glucagon secretion was significantly lowered in patients with overt diabetes, compared to patients with primary diabetes (insulin-dependent and non-dependent diabetes mellitus) and healthy controls [38]. However, in a small study of 10 patients with CP – examined with an arginine test – the authors reported that the pancreatic glucagon showed a brisk early increase greater than that seen in normal subjects [39]. It has also been suggested that protein and amino acid malabsorption in CP further decreases the glucagon secretion [40].

The destructive processes characterizing CP also affects the PP-secreting cells in a way parallel to that of  $\beta$  cells [41, 42]. The overall clinical importance of this effect is not completely clarified. It is known that glucagon, PP and somatostatin inhibit pancreatic exocrine secretion while insulin potentiates the stimulatory effect of CCK on pancreatic enzyme secretion. Pancreaticobiliary secretions initially release PP, which in turn inhibits pancreatic secretion. Thus, deficiency of pancreatic enzyme secretion into the duodenum in conjunction with the direct structural lesion of the polypeptide-secreting cells seem to be the reasons for the decreased PP release in CP [42]. In contrast, increased plasma concentration of somatostatin was found in patients with insulin-dependent

diabetes secondary to CP and this may contribute to a reduction in overall blood glucose level in insulin-depleted patients, probably due to the inhibition of glucagon secretion [41].

### **Pancreatic Diabetes**

Diabetes due to pancreatic disease is reported as accounting for about 0.3% of diabetic patients, but the frequency is dependent upon the prevalence, awareness and diagnostic pick-up rate of pancreatitis in different geographical areas. In heavy drinking populations, the frequency is probably in the vicinity of 1%. Also, geographical and environmental considerations are important in directing the investigative profile in a diabetic population.

The incidence of diabetes in CP is dependent on several factors, such as etiology, presence or absence of pancreatic calcification and the duration of the disease [32], and is approximately 60% [41]. However, pancreatic inflammation as a causative factor accounts for only 1% [43]. The types of diabetes secondary to CP have also been described but the data are conflicting. Among 88 patients with CP, Larsen et al. [20] found 35% to be IDDM and 31% NIDDM or IGT, while according to the large Japanese study of Okuno et al. [44], IDDM was detected in 30% and NIDDM in about 50% of patients with CP. However, the incidence of diabetes might actually be more frequent, since endocrine dysfunction could sometimes represent the first clinical sign of pancreatitis, in the absence of other characteristic symptoms of the disease [45].

On the other hand, impaired exocrine pancreatic secretion has frequently been observed in diabetic patients via different diagnostic methods, including direct and indirect function tests [35, 45, 46]. The prevalence of CP among 17,500 diabetic patients in Japan was 1.71% [44]. In contrast, in 148 IDDM and NIDDM patients ductal morphological changes, characteristic of CP, have been detected with ERCP in a large percentage of patients (76%) independently from diabetes duration and treatment [45]. The measurement of fecal elastase has been used to assess the exocrine function in a study population of more than 1,000 patients with type 1 and 2 diabetes [35, 46]. Impaired pancreatic function was revealed in a high percentage of patients, particularly in those with long-lasting diabetes. One could hypothesize that exocrine pancreatic failure could represent a complication of diabetes due to autonomic neuropathy and arterial le-

sions, but the correlation between diabetes duration and low fecal elastase concentration was weak, whilst similar exocrine insufficiency was observed even in diabetic patients without evidence of angiopathy [46].

Taken together, these data suggest that a substantial number of patients might have both diabetes and CP. Furthermore, CP might constitute the cause of diabetes in several cases, though it is an uncommon disease. Nevertheless, the complicated methods of investigation used in the past and the fact that CP leads to clinical manifestations very late in the time course of the disease might have resulted in underestimation of the prevalence of the disease.

Bank et al. [32] studied 1,235 patients with nonmalignant diseases of the pancreas in a follow-up of 5–12 years and concluded that diabetes (a) is more common in ACP; (b) rarely occurs after the first attack, though its prevalence increases with time, and (c) rises markedly in calcific pancreatitis.

Symptomatic diabetes is frequently present in alcohol-induced calcific and noncalcific CP as well as in noncalcific tropical CP. The incidence is lower in idiopathic pancreatitis and uncommon in miscellaneous cases [32]. In about 90% of patients with calcific pancreatitis in most Western countries, alcohol abuse is the commonest cause; whether the pre-existence of hepatic and nervous malfunction due to alcohol abuse in these patients in conjunction with severe malnutrition could influence the endocrine function of the pancreas is unclear.

It is of interest that all the complications of CP are considerably higher in patients with radiological calcification, and this is particularly evident with regard to endocrine dysfunction. It has been reported that both insulin and glucagon secretion are disturbed more strongly in calcific than in noncalcific pancreatitis [38]. The incidence of overt diabetes was 30% in noncalcific CP, as compared to 70% in calcific pancreatitis [32]. In addition, in patients with precalcific disease followed up to the calcific state, the incidence of abnormal glucose tolerance increased from 70% at the time of radiological normality to 91% at the time of radiological calcification [32]. According to a more recent prospective study concerning 500 patients with CP followed up over a mean period of  $7.0 \pm 6.8$  years, the risk of diabetes increased more than 3-fold after the onset of pancreatic calcifications [47].

Fasting serum C-peptide levels were significantly diminished in patients with CP, diabetes and pancreatic calcification, diagnosed by ultrasonography compared with the measured levels in patients with protein-deficiency pancreatic diabetes [48]. It has been hypothesized

that in calcific pancreatitis there is actual damage of  $\beta$  cells, whereas in noncalcific pancreatitis there may be involvement of ischemia or functional derangement of the islets without destruction of the cells [38].

### **Differences between Pancreatic and Idiopathic Diabetes**

The common symptoms of pancreatic diabetes do not differ from other diabetic states: polyuria, polydipsia, and polyphagia may develop gradually or rapidly. Ketosis and diabetic coma are uncommon in CP patients and can be signs of the presence of a serious intrapancreatic or systemic infection, such as cholangitis, pneumonia, or pulmonary tuberculosis. This difference may be related to the nonavailability of fat stores in these patients and to the fact that the secretion of insulin, in spite of being markedly diminished in CP, is almost never totally absent. On the other hand, even a small quantity of exogenous insulin may induce profound hypoglycemia, because insulin effects remain unopposed due to glucagon deficiency [32, 49–52].

Initial studies showed that diabetic retinopathy is a rare complication of pancreatic diabetes, occurring in 7.4–18% of cases [53, 54]. However, comparison of the incidence of this complication in patients with type 1 diabetes with a group of CP patients indicated no difference in the risk for retinopathy in these two groups; the duration of known diabetes was on average 6.6 years, that is, similar to that in the first group [55]. Neuropathy has been reported in about 30% of patients with CP and overt diabetes by electromyography [32]. Neuropathy is almost always present by the time clinical symptoms of diabetes appear. The early onset may be related to the fact that peripheral nerves had already been subclinically affected by long continued alcohol abuse or suboptimal nutrition.

According to a retrospective study, which included 83 patients with diabetes due to CP, lower-extremity arteriopathy (assessed by noninvasive tests) had the same prevalence and distribution in CP and idiopathic diabetes patients, despite the different risk factors for vascular disease in the two groups [56]. This observation emphasizes the pivotal role of chronic hyperglycemia and its duration in the pathogenesis of macroangiopathy in diabetic patients [56].

Although extremely rare in the Western world, tropical CP represents a common juvenile form of CP in many tropical developing countries, which leads to severe mor-

bidity in a large proportion of affected patients [57]. Microvascular complications occur in fibrocalculous pancreatic diabetes (the diabetic stage of tropical CP) as frequently as in other primary forms of diabetes; however, macrovascular complications are uncommon [58]. Nevertheless, the overall prognosis for patients with fibrocalculous pancreatic diabetes appears to have improved, possibly because of earlier diagnosis, better management of diabetes and improved nutrition [57, 59].

Diabetes associated with autoimmune CP is an uncommon clinical entity, probably caused by T-cell-mediated mechanisms primarily involving islet  $\beta$ -cells as well as pancreatic ductal cells [60, 61]. Initial reports correlated some cases of CP with Sjogren's syndrome and primary sclerosing cholangitis, on a common basis of an unknown autoimmune mechanism [62, 63]. Intra- and perinsular mononuclear cell, mainly CD8+ T cell, infiltration, as well as mononuclear cell infiltration around the ductal cells, have been histopathologically demonstrated by biopsy in diabetic patients with autoimmune CP [64]. Treatment with prednisolone subsequently improved insulin secretion and glycemic control in these patients [65]. Due to its rareness and clinical features (inguinal lymphadenopathy, hypergammaglobulinemia), autoimmune pancreatitis can be misdiagnosed or confused with primary pancreatic lymphoma [66] and pancreatic malignancy [67].

### **Enteroinsular Axis and Metabolic Abnormalities in CP**

The term enteroinsular axis refers to the signaling pathways between the gut and the pancreatic islets that enhance the insulin response to absorbed nutrients [68]. Glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 are the most important insulin-releasing hormones (incretins) in this axis and are released rapidly after meals. The biological effect of these peptides is partly regulated through metabolism by dipeptidyl peptidase IV, an enzyme that cleaves the first two amino acids from both glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 and hydrolyzes the active molecules into biologically inactive NH<sub>2</sub>-terminally truncated fragments [69]. The physiological role for incretins in the enteroinsular axis has been established; however, the involvement of these hormones in pathological situations, such as CP, is equivocal. The potential disturbances of the enteroinsular axis in the issue of pancreatic diabetes were initially examined in the seventies. In pa-

tients with CP receiving an oral glucose load or mixed liquid test meal, glucose-dependent insulintropic polypeptide levels have been shown to be significantly elevated [70], although insulin response was qualitatively similar but quantitatively lower, compared with normal subjects [71]. More recent studies have indicated the modulation of the enteroinsular axis by a number of cofactors, (bowel or stomach resection, type of nutrient, medication). Furthermore, new gut hormones (e.g. ghrelin, peptide YY) and neuropeptides (e.g. neuropeptide Y), which are multilaterally involved in the complex connection between insulin regulation, adipose tissue and food intake, have been introduced [72]. The ascertainment that body weight is generally reduced in CP [73] together with the observation that pancreatic enzyme replacement therapy results in a significant gain in body weight (although not improving the endocrine profile) of patients with pancreatic diabetes [74] indicate the necessity for further investigation in order to elucidate the impairment of the enteroinsular axis in CP.

Apart from the parallel constructive disruption of the endocrine and exocrine pancreas, metabolic abnormalities seem to signify an additional common link of both endocrine and exocrine dysfunction in CP [42, 75]. It has been shown that the plasma zinc concentration was below normal in CP patients and that plasma selenium concentrations were lower in CP patients than in healthy controls [76]. The occurrence of diabetes in these patients further increases zinc and selenium deficiencies [76]. On the other hand, dietary selenium supplementation increases the peroxisomal  $\beta$ -oxidation [77] and its serum concentration in healthy subjects is a predictive variable of the unsaturated index of plasma phospholipids [78]. Moreover, low levels of linoleic acid were observed in patients with pancreatic diabetes probably due to fat malabsorption [35]. Although the clinical relevance of such deficiency has not been evaluated in the issue of CP, it is well established that the decrease of linoleic acid, relative to the saturated fatty acid intake, is associated with coronary heart disease mortality in the general population [79]. This deficiency in CP may be implicated in the acceleration of atherogenesis in this population [35, 80], although LDL cholesterol and apolipoprotein B are lower in patients with pancreatic diabetes compared with patients with idiopathic diabetes [56].

During insulin deficiency, proteolysis and the flux of amino acids into extracellular space increase, while amino acid transport rates into the intracellular space decrease [75], resulting in an increase in plasma concentration of many amino acids, particularly of the branched chain ami-

no acids. In addition, glucagon deficiency could also affect amino acid metabolism by increasing their levels, regardless of blood glucose concentrations [75]. These observations suggest a regulatory role of both insulin and glucagon in amino acid metabolism, which is impaired in CP.

### **Correlation between Endocrine and Exocrine Insufficiency**

Morphological studies have documented qualitative and quantitative changes in endocrine pancreas in parallel with exocrine tissue injuries [41, 81]. In addition, parenchymal destruction and peri-insular sclerosis may alter local circulation and glucose diffusion [42]. Concomitant alterations in both exocrine and endocrine pancreas could be logically explained in CP caused by viral infections or autoimmune disease, since the pathological process is diffuse and affects the whole gland. It has been hypothesized that in CP of other origin the primary damage of duct cell structures and the following presentation of structural proteins to the immune system may lead to the stimulation of autoimmunity against both exocrine and endocrine tissue [45]. In consistency with this purpose, autoantibodies against exocrine tissue have been observed in patients with insulin-dependent diabetes [82]. Of interest, rapid onset of diabetes has been reported in 11 of 56 Japanese patients with type 1 diabetes, without diabetes-related serum antibodies but markedly elevated serum pancreatic enzyme concentrations [83]. Although the precise mechanism of  $\beta$ -cell destruction in patients with this new nonautoimmune entity of diabetes is not known, the presence of lymphocytic infiltrates in the exocrine pancreas seen in the biopsy specimens emphasizes the close linkage between exocrine and endocrine functional disruption.

Andersen et al. [84] observed impaired C-peptide response after stimulation with oral glucose and a parallel decrease in the secretion of both amylase and lipase after a test meal was given in patients with CP. The same authors reported that patients with insulin-treated diabetes secondary to CP had a residual insulin secretion similar to that noticed in patients with type 1 diabetes.

In order to assess the potential correlation between endocrine and exocrine dysfunction, patients with CP were divided into two groups, depending on the appearance of steatorrhea, and serum PP levels were measured after stimulation with secretin. Results showed that PP levels were significantly lower in patients with steatorrhea. Earlier studies using measurements of insulin and

pancreatic enzyme response to oral glucose or a test meal [85, 86], in nonobese patients with CP and negative family history of diabetes, had also shown a similar parallel loss of endocrine and exocrine function during the course of CP. A close correlation was found between the insulin response to oral glucose and the exocrine function measured as the concentration of pancreatic enzymes in duodenal juice after intravenous cholecystokinin-pancreozymin administration [85].

In addition, a significant difference was found in the insulin levels measured after a test meal in patients with CP and severe maldigestion (steatorrhea >20 g/day) as compared to those who had mild maldigestion (steatorrhea <10 g/day) [86]. However, the degree of exocrine dysfunction cannot always be predicted by the presence of steatorrhea. It has been reported that a number of patients with normal fat excretion had severely reduced enzyme secretion after a secretin-pancreozymin test and vice versa [87]. A close correlation between amylase output and the decrease in daily urinary C-peptide excretion has also been reported [38]. The lowered increase in glucagon and C-peptide concentrations during arginine test was correlated significantly with the impaired exocrine function as assessed using the urinary para-aminobenzoic acid excretion after an oral ingestion of N-benzoyl-L-tyrosyl-p-aminobenzoic acid [88]. Furthermore, glucagon and C-peptide secretion was impaired only in patients with moderate and severe CP, staged by endoscopic retrograde pancreaticography [88].

The above reports support the contention that there may be parallel destruction of islets and acinar cells in the course of CP. In other studies, it was shown that overt diabetes occurred when trypsin output was decreased to 10% or less of normal [89], and that the PP response was impaired only in the presence of severe or moderate exocrine pancreatic insufficiency [90].

### **Pancreatic Surgery**

Two types of operation are widely used, drainage procedures and resections. Drainage operations preserve pancreatic tissue with good early results, which often worsen progressively the longer the follow-up, while resection allows effective control of the complications of CP, but is generally associated with more exocrine and endocrine insufficiency as a consequence of removal of pancreatic tissue. However, safer procedures have been developed for the duodenum-preserving pancreatic head resection [91].

The influence of pancreatic surgery on the appearance of diabetes mellitus in patients with CP is not clear. Ammann et al. [92] in a large prospective study published in 1984, reported that approximately 1 of 2 patients suffering from ACP needed pancreatic surgery due to recurrent or persistent severe pain, mainly caused by pseudocysts. According to that study, no marked difference between operated and nonoperated patients or between types of operation were revealed. Interestingly, the proportion of patients experiencing lasting pain relief was similar in the operated and nonoperated group of patients and it was correlated with the duration of the disease. Noticeably, pain relief was accompanied by an increase in pancreatic exocrine dysfunction and calcification [92]. The same group of investigators reported that the progression of endocrine dysfunction was similar in surgical and non-surgical patients, approximately 50% at 10 years of onset [31].

In a recent prospective cohort study including 500 patients, the prevalence of diabetes in patients who underwent elective pancreatic surgery compared with that in patients who were never treated surgically was similar, with the exception of those who had undergone distal pancreatectomy [47]. About 57% of these patients developed diabetes mellitus within 5 years after surgery, while incidence was significantly lower in other surgically managed groups (pancreaticoduodenectomy  $36 \pm 18\%$ , pancreatic drainage  $36 \pm 13\%$ , and  $24 \pm 7\%$  where cystic, biliary or digestive drainage was performed) [47]. Thus, distal pancreatectomy is considered as an independent risk factor for the development of diabetes in CP. It has been assumed that pancreatic duct obstruction plays a minor role in the appearance of diabetes compared with parenchymal destruction and, if feasible, surgical procedures should preserve sufficient endocrine pancreatic tissue [47].

It has been maintained that lateral pancreaticojejunostomy, although improving the exocrine pancreatic function in chronic alcoholic pancreatitis, does not affect the endocrine function [93]. Several authors [91, 94, 95] reported no negative influence of duodenum-preserving resection of the head of the pancreas (DPRHP) on endocrine pancreatic function in the majority of treated patients, possibly due to the prominent localization of Langerhans cells in the tail of the organ. Similarly, according to the findings of Maartense et al. [96], blood glucose levels did not change after DPRHP, but a significant reduction in serum C-peptide and glucagon levels and a reduction in peak plasma PP levels were observed. This finding was expected because PP-secreting cells are local-

ized especially in the pancreatic head. More patients became insulin dependent after DPRHP [96], possibly because DPRHP influences the secretion of the regulatory peptides (glucagon, somatostatin and PP) from the pancreas.

In order to determine if there is any difference in pancreatic function after pylorus-preserving pancreatoduodenectomy according to the type of pancreatoenterostomy (pancreatojejunostomy, P-J or pancreatogastrostomy, P-G), 28 patients without preoperative diabetes were evaluated 1 year after surgery [97]. Severe exocrine and endocrine pancreatic insufficiency developed after preserving pancreatoduodenectomy in both the P-J and P-G groups, but there was more functional deterioration in the P-G group than in the P-J group. On GTT, 43.8% (7/16) of the P-J group had abnormal results after surgery, whereas 75.0% (9/12) of the PG group had an abnormal postoperative GTT. Although the difference in the number of patients with IGT in the two groups did not reach statistical significance, serum glucose levels 30 and 60 min later were higher in the P-G group than in the P-J group [97]. These data are in agreement with the study of Maartense et al. [96] who reported that clinical endocrine function, reflected by blood glucose levels, had improved after pancreatojejunostomy. In contrast, other authors have shown deterioration in endocrine function after a drainage procedure [98, 99]. In a recent comparison study of the operative management of patients with CP, Frey and Mayer [100] concluded that, concerning the endocrine function, the local resection of the head of the pancreas combined with longitudinal pancreatojejunos-

tomy (LR-LPJ) and the DPRHP have some advantages over preserving pancreatoduodenectomy [100].

More recent studies have also attempted to compare the potential benefits of various surgical procedures in the endocrine function of the pancreas [97, 101], but the available documents do not yet suffice to establish a therapeutic guideline.

The above line of data indicates that the decision for pancreatic surgery should be taken with caution, especially in uncomplicated patients.

### Concluding Remarks

It has been recognized for many years that establishing a diagnosis of CP may range from a simple task to an immensely challenging and intensive process. Pancreatic endocrine insufficiency is usually a very late consequence of CP, hence the impairment of the basal levels of glucose and insulin usually reveal the disease at an advanced stage. Functional endocrine insufficiency will develop in approximately 2/3 of patients with chronic disease and may be present even in the absence of pain. The symptoms primarily manifest as hyperglycemia; however, the development of diabetic ketoacidosis is rare. Many patients with CP have an insufficiency of glucagon and, concurrently, are malnourished, so hypoglycemia may also develop. Further investigation and larger controlled studies must be performed in order to work out common criteria for the diagnosis of endocrine insufficiency in CP and the follow-up of its course.

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