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Pancreatic Head Mass: How Can We Treat It ? Chronic Pancreatitis: Conservative Treatment

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The main goal of conservative treatment for chronic pancreatitis is to relieve pain and prevent or substitute functional insufficiency without surgery. Pain and functional deterioration in chronic pancreatitis is multifactorial. Intermittent attacks of pain with temporary functional deterioration may originate from recurrent tissue necrosis and inflammation provoked by alcohol consumption or other causes of recurrent pancreatitis, while chronic pain with progressive pancreatic insufficiency may be secondary to segmental hypertension due to ductular strictures and stones [1]. The chronic inflammatory process may also involve increased intrapancreatic pressure [2] with ischemia [3], neural inflammation and scarring [4], intra - and peripancreatic fluid collections and pseudocysts [5], common bile duct stenosis and/or duodenal compression [6] and papillitis [7], all resulting in the precipitation of relapses and fluctuating pain. Both the inflammatory process and ductular hypertension can diminish with the development of severe pancreatic insufficiency and the pain may disappear in several cases [8]. It seems that the "burned out" state of pancreatitis, if it occurs, takes more than 10 years and the balance is distorted with an almost total loss of exocrine and endocrine function with severe diabetic and/or alcoholic neuropathy and malnutrition. Surgery in alcoholic patients may accelerate these processes [8]. The capability of the pancreas to regenerate is well demonstrated in animal studies [9, 10] as well as in patients with chronic pancreatitis [11-14] However, even after longitudinal pancreaticojejunostomy [15] or after the more sophisticated duodenum-preserving resections of the head of the pancreas [16, 17], some pancreatic tissue is lost and gastrointestinal integrity and/or motility is altered. Early and late morbidity with some mortality, a rather long hospital stay and the additional expenses of everlasting substitution therapy stimulate intensive research for new interventional procedures to relieve pancreatic pain and prevent functional deterioration without surgery.

Occlusion Therapy

To achieve the "burned out" state of chronic pancreatitis, occlusion of the pancreatic duct has been carried out by means of surgery or via endoscopic canulation of the papilla of Vater [18]. It was stated that the number of relapses diminished somewhat after these procedures, but functional changes of the pancreas have not been examined.
In our study [19], complex monitoring of exocrine (secretin-pancreozymin and/or Lundh tests, starch tolerance and Lipiodol tests, fat balance) and endocrine (glucose tolerance) functions was performed before and/or after occlusion of the pancreatic duct in 15 patients. Endoscopic occlusion was carried out using Ethiblock [20]. In 6 cases, the pancreatic duct was filled with Ethiblock or Neopren during surgery. In these patients, simultaneous ligature completed occlusion of the pancreatic outlet while the opening of the common bile duct was assured by papillotomy. Temporary obstruction of the pancreatic duct did not result in any long-lasting symptom- and relapse-free situations

in most of the patients with chronic relapsing pancreatitis. The secretory capacity of the pancreas measured by different indirect and direct tests did not diminish sufficiently even after the surgical procedure. The uneven results of occlusion treatment may be explained by the rapid recanalization of the pancreatic duct caused by the high secretory pressure of the pancreas pushing out the glue through the loosened ligature. The Santorini duct may provide an alternative route for this movement as was observed endoscopically in one patient.

Regained secretory capacity of the pancreas may not be the sole factor provoking further relapses, and alterations of the duct system may interfere with secretory changes.

The main advantage of endoscopic treatment was that it did not need surgical intervention and in cases with uneven results it could be repeated.

In the cases of severe pancreatic insufficiency with significantly decreased secretory pressure, the results seem to be better and the risk of acute pancreatitis provoked by partial obstruction diminishes. Therefore, previous functional examination for the selection of patients seems to be mandatory.

Jejunal Feeding for Chronic Pancreatitis with Severe Necrosis

In pancreatitis, total parenteral nutrition was shown to enhance bacterial translocation through the atrophied bowel wall. Jejunal feeding seems to maintain the physiological motility of the gut, to prevent atrophy of the villi, to increase mesenteric circulation and to put the pancreas into rest. The slow, continuous infusion of nutrients did not interrupt the pancreatic volume and bicarbonate changes characterizing the interdigestive phases, "postprandial" peak and integrated secretions were the same as during basal secretion [21].

We have developed an endoscopic technique to place the naso-jejunal tube into the second loop of the jejunum through the working channel of the endoscope with the aid of a guidewire and pusher [22]. Using this technique, jejunal perfusion can be carried out without delay, and the pain regularly disappears in 1 to 2 days while the acute fluid collections and inflammatory alterations are resolved in 1 to 2 weeks.

In cases of chronic calcifying pancreatitis, serious necrosis can develop in the residual pancreas, resulting in acute pancreatitis-like disease. Using nasojejunal tube feeding, a better healing rate can be achieved with less endoscopic intervention or surgery than in the parenteral nutrition group. Duration of nutrition and hospitalization is shorter. Financially, jejunal feeding is better than parenteral nutrition.

In our series of 19 patients, the computed tomography scans also showed more than 20% necrosis in the residual pancreas. In 12 cases, jejunal feeding was used for nutrition via an endoscopically placed nasojejunal feeding tube. In this group, only 2 patients were operated on because of complications from pancreatitis. In 7 cases, hypocaloric parenteral nutrition was used for feeding. In this group, 4 patients were operated on and 1 patient required endoscopic intervention.

Endoscopic Papillotomy for Chronic Pancreatitis

The incidence of common bile duct stricture due to fibrosis and/or inflammation requiring biliary bypass may be as high as 57% [6]. Endoscopic papillotomy with biliary stent placement, with or without nasobiliary lavage for prevention and treatment of cholangitis, can render surgery unnecessary [23], but clogging of the endoprosthesis with suppurative cholangitis is a frequent complication during the long period necessary for recovery. During a 4-year period, 62 patients with biliary stenosis due to chronic calcifying pancreatitis were stented in our institution. 32% had had previous pancreatic surgery. The cause of biliary obstruction was chronic calcifying pancreatitis with (24%) or without (56%) pseudocyst in the head of the pancreas or with acute relapse of the disease (11%) and chronic obstructive pancreatitis (8%). Forty-eight patients received a simple 10F drain as a result of a recent attack of chronic pancreatitis. In 16 patients with more

stable chronic calcifying pancreatitis, a second large stent, and in 2 similar cases three 10F stents, were placed into the common bile duct during a 3-6 month accommodation period. In 10 patients, a jejunal tube for jejunal feeding was placed at the same endoscopy to accelerate recovery from the relapse of the disease. In 18 patients, temporary naso-biliary drainage was necessary to prevent suppurative cholangitis and early clogging of the stents. Patients were monitored by ultrasonography and laboratory tests every 3 months, and by endoscopic retrograde cholangiopancreatography every 6 months. Stent obstruction occurred in 34% of the cases with one drain in place. The others recovered from the biliary stenosis or they were supplied with a second stent. Biliary drainage remained satisfactory for more time in the patients with multiple stents and occlusion occurred only in 17%. It seems that endoscopic stenting can replace surgical bypass for biliary stenosis caused by chronic pancreatitis. Multiple stents may dilate the strictures progressively and remain patent for the long recovery period necessary to stabilize this progressive chronic disease.

Characteristic to chronic obstructive pancreatitis is difficulty in pancreatic outflow which increases ductal pressure resulting in alterations of ductular permeability, periductular inflammation and fibrosis with dilatation of the main pancreatic duct [24]. Release of the obstruction with pharmacological therapy (nitrates, phosphodiesterase inhibitors, calcium antagonists, β2 agonists [25] in Type III sphincter of Oddi dysfunction or with surgical or endoscopic double papillotomy in Type II and Type I papillary stenosis) can relieve pain and ameliorate outflow and pancreatic function. The diagnosis of pancreatic sphincter of Oddi dysfunction is based on evocative tests: Nardi test, fatty meal or secretin ultrasonography with laboratory measurements and nitrate administration with/or without hepatobiliary scintigraphy and endoscopic manometry [7].

In chronic obstructive pancreatitis due to primary odditis not responding to pharmacological therapy, the treatment of choice is the endoscopic double papillotomy. According to our "old" technique [26], classic endoscopic papillotomy of the biliary sphincter is followed by endoscopic septotomy only after several months in order to avoid pancreatitis in these vulnerable cases. Pain and amylase elevation in response to the Nardi test (prostigmine-morphine provocation; [7]) were only temporarily diminished after biliary papillotomy but a definitive symptom free state and functional recovery occurred only after papillotomy of the sphincter pancreaticus proprius. Functional and morphological results of surgical and endoscopic double papillotomy seem to be comparable [27]. Although surgical cases in our study were already in somewhat more advanced stages than the endoscopic ones before surgical intervention (more calcification and other alterations needing supplementary surgery), the pancreatic function proved to be surprisingly good after both double sphincterotomies.

Pancreatic enzyme secretory responses to the Lundh meal were increased by +61% and +67% at the first check-up after surgical and endoscopic double sphincterotomy, respectively, which was further ameliorated by achieving +115% at the second follow-up examination. The endoscopic double papillotomy better prevented the painful relapses and functional deterioration of chronic obstructive pancreatitis than the surgical one because the earlier intervention resulted in better decompression of the whole ductular system.

Endoscopic Drainage of the Pancreatic Duct with Extracorporeal Shock Wave Lithotripsy (ESWL) and/or Lavage

Endoscopic therapies have been used with the aim of alleviating ductal obstructions caused by strictures and stones. Strictures may be treated by balloons or dilating catheters but it is better to follow dilation by stent placement across the stricture [28, 29]. The stent has to be removed as soon as possible because of regular clogging after 2 to 6 months. In addition, aggravation of ductographic changes

may develop during the stent treatment [30]. Endoscopic techniques also have been used for the removal of pancreatic stones after endoscopic sphincterotomy with or without fragmentation by ESWL [31, 32].

In 3 months, six patients with chronic calcifying pancreatitis were treated with this new method in our institution. Before the treatment, we carried out endoscopic sphincterotomy and septotomy in the pancreatic duct, in order to accelerate stone delivery. In most cases, we inserted a nasoductal catheter into the pancreatic duct for citrate lavage for a number of days. We performed the ESWL with Midazolam and Pethidine premedication in 1-3 seanses (15 kV, 1500 beats). In one of the 6 cases, this intervention was unsuccessful. In all other patients, the intraductal stones disappeared or significantly disintegrated and the diameter of the ducts diminished.

In these cases, the endoscopic papillotomy can be performed directly through the pancreatic duct because of the partial "burned out" state of the disease which may also explain that the shock waves rarely aggravate pancreatitis. In our practice, pancreatic papillotomy is performed only in patients with dominant stricture at the level of the papilla. In other cases, nasopancreatic drainage is performed with a 5 to 7F catheter without papillotomy for lavage with citrate. In vitro dissolution of human pancreatic stones with a highly diluted citrate solution was demonstrated by the Marseille team [33]. During a 2-year period we performed 9 nasopancreatic drainages in 8 patients with chronic calcifying pancreatitis [34]. The pancreatic duct was continuously perfused with a 50% mixture of isotonic citrate and saline at an increasing rate of 1 to 3 mL/min. for 4 days. A stone-free state of the main duct was achieved in all but 2 cases. Pancreatic pain disappeared on the second day of perfusion and the patients remained pain free for the 1-3 years of the follow-up period. Pancreatic function controlled with Lundh test before and repeatedly after perfusion in 5 patients recovered by +122% (range 0-360%). In one female patient, enzyme secretory capacity increased by +189% immediately after treatment and it further ameliorated by +360% during the next 3 months and remained stable until the end of the 27-month follow-up period. In 2 cases, no functional recovery occurred although the pain disappeared at least until their 1-year follow-up.

Complications of lavage (temporary pain with amylase elevations at high levels in one and fever in another case in our study) are rare and mild; the procedure can be repeated if the pain eventually returns. This non-surgical technique can be tried as a first step to relieve pancreatic pain provoked by intraductal strictures and/or stones.

Endoscopic Decompression of Pseudocysts

Most patients with pancreatic pseudocysts have pain and other complications. Computed tomography and/or ultrasonography assure precise localization. Chronic pseudocysts immediately adjacent to the stomach or duodenum can be treated with internal drainage via endoscopy. Using the bulging of the pseudocyst on the wall as a guide, the cyst is punctured with a diathermy needle and then the hole is extended with a sphincterotome or by dilation and drained with a nasocystic and/or internal drain [35, 36]. Percutaneous techniques are also frequently used [37].

We have developed a combined technique composed of percutaneous ultrasound guided fine needle puncture, aspiration of a 10-20 mL fluid sample for biochemical and cytological examinations, filling the cyst with 10-15 mL of contrast material followed by X-ray guided endoscopic diathermic needle puncture of pseudocysts located 1 to 4 cm from the gastric or duodenal wall and nasocystic and/or internal drainage with 8-10F catheter [38].

Up to the present time, we have performed more than 120 cystenterostomies using this method. In one third of them, there was no clear bulging into the stomach or duodenum and the pseudocyst was 1-3 cm away from the wall. Complications were not increased with increasing distance within such limits. One perforation and one bleeding required

surgery. Two patients died, one after surgery as a result of cardiac insufficiency and the other due to endotoxin sepsis in spite of successful drainage of the infected pseudocyst.
The endoscopic cystogastrostomy and cystoduodenostomy are good alternative treatments to surgical and percutaneous drainage.

Percutaneous Celiac Plexus Block (PCPB) for Pancreatic Pain

Symptomatic treatment of pain, the most devastating symptom of chronic pancreatitis, should involve a method which needs no surgery, has a success rate of over 80% with long-lasting effects but which can be repeated without side effects if the pain eventually returns. The PCPB block seems to fulfill these criteria [39].
In a study at the Mayo Clinic [40], we have reevaluated the effectiveness of a celiac plexus block in chronic pancreatitis.
Three types of PCPB were applied to the patients:

1. Diagnostic PCPB with two 15 mL injections of 0.5% bupivacaine (Marcaine) alone.
2. Therapeutic PCPB with two 15 mL injections of 0.5% bupivacaine followed by two 10 mL injections of absolute alcohol.
3. Therapeutic PCPB with two 15 mL injections of 0.5% bupivacaine mixed with 40-120 mg of triamcinolone diacetate or methylprednisolone acetate.

When only the local anaesthetic bupivacaine injected into the celiac plexus, only temporary pain relief lasting for several hours or days was obtained.
Alcoholic PCPB resulted in long lasting pain relief. Pain relief was about the same after the second treatment as after the first. The long acting steroids significantly prolonged the duration of pain relief as compared to that achieved with the diagnostic PCPB. Triamcinolone diacetate and methylprednisolone acetate resulted in about the same pain relief; moreover, there was no correlation between the dose of steroids (40-120 mg) and the duration of the pain free period after blocks. In 75-81% of patients, the pain relief was total for about 3-5 months. Repeated blocks were as effective as the first; unsuccessful treatments were followed by injections which were effective Duration of pain relief after alcoholic PCPBs applied to CP patients was significantly longer than that by steroid blocks. In calcified chronic pancreatitis, with diabetes which required insulin, the steroid PCPB was more effective than in non-calcified, non-diabetic patients.
The steroid PCPBs seem to be advantageous in chronic pancreatitis patients in whom a series of blocks are necessary because of the long duration of painful periods of the disease. In these cases, blocks can present an opportunity of avoiding surgery and/or irreversible damage, and fibrosis of the celiac plexus thought to be provoked by alcoholic blocks.

Management of Pain and Functional Deterioration in Chronic Pancreatitis

In our practice, when a patient with chronic pancreatitis presents with pain or a changeable pain pattern and/or deterioration of pancreatic function, we try to determine structural alterations behind the progression (inflammation, pseudocyst, papillitis, stricture or stone) and intend to treat them interventionally [34]. For further regeneration of the pancreas, we used to use intranasal CCK-OP drops [12] and/or soybean treatment [13] with promising results, but registration of these treatment modalities failed because of fear of cancer, although in ductular cancer models, CCK and soybean, releasing endogenous CCK do not stimulate but inhibit pancreatic cancer development.
We advise patients to cease all alcohol intake and smoking, administer fractional insulin and large doses of exogenous enzymes and some non-narcotic analgesics if necessary. If this program for pain relief and functional recovery does not work, we try percutaneous celiac plexus blocks with long-lasting

steroids. Only if all of these treatments fail, do we recommend surgery.

Substitution Therapy in Steatorrhea

Manifestation of pancreatic insufficiency depends on pancreatic function as well as on gastrointestinal motility, gastric, biliary and intestinal secretions, absorption, hormone releases and postoperative situations. The secondary factors may require special corrections to achieve significant amelioration of resistant steatorrhea.

Supplying enough lipase into the duodenum to achieve more than 5-10% of normal enzyme concentrations is associated with abolition of steatorrhea in most cases [41]. However, recovery experiments in patients who ingested different preparations have demonstrated uneven lipase and somewhat more trypsin and amylase activities in the duodenum [42, 43]. There are two factors involved in the rapid disappearance of enzyme activities during their passage of intestinal tract: gastric acid secretion and proteolytic inactivation.

Gastric Function and Duodenal pH

In alcoholic chronic pancreatitis, when the food has been emptied, gastric secretion is not further buffered by meal, and intragastric, then intraduodenal pH falls to 4 or less as delivered acid cannot be equilibrated by decreased bicarbonate secretion of the diseased pancreas [44]. The low duodenal pH decreases micellar concentrations of bile acids and lipids by precipitating bile acids, although postprandial secretion of bile is normal in patients with pancreatic insufficiency. Raising intraduodenal pH by giving H_2-blockers prevents precipitation of bile acids and improves lipid digestion [45].

The major problem with unbuffered postprandial gastric secretion in pancreatic insufficiency is that the decreased duodenal enzyme activity delivered by the diseased acinar cells can be further diminished by acid inactivation. Amylase and lipase are more sensitive to low pH. Between pH 5 and pH 4, first amylase and then lipase is inactivated irreversibly while trypsin activity still remains intact [46]. Therefore, acid inactivation of lipase can only partially explain the uneven results of substitution therapy in steatorrhea when azotorrhea and carbohydrate malabsorption do not present a problem in the same patients. H_2-blockers antacid therapy was proposed and used as adjuvant treatment but published results are contradictory [47] and total abolishment of steatorrhea was only rarely achieved using different although gastric and duodenal pH was maintained above pH 5 for a long time [41]. Results of replacement therapy [48] and duodenal recovery of enzymes [43] was not influenced by hyperacidity or anacidity of patients, and bypassing the stomach by duodenal application of Viokase did not abolish steatorrhea better than oral therapy [49]. Enteric coated tablets protecting the preparates from acid secretion of the stomach proved useless, and only newer microspheres resulted in dose-dependent amelioration of steatorrhea [50, 51]. Finally, acid stable fungal lipase proved not to be more effective than the enteric coated microspheres in ameliorating steatorrhea [52].

Proteolytic Inactivation of Lipase

The role of pepsin in addition to that of acid in the inactivation of pancreatic enzymes has been previously investigated [41, 44] but its clinical significance has not been separately proven. Using in vitro experiments, we have demonstrated that rapid inactivation of lipase of different pancreatin preparations was in an inverse relationship with trypsin activation, and inhibiting trypsin activity with soybean trypsin inhibitor significantly prolonged survival of lipase during incubation in buffer solution and in secretin-pancreozymin or Lundh test-meal stimulated duodenal juice [53]. The lipase activity of secretin-pancreozymin stimulated duodenal juice decreased faster than that stimulated by the Lundh meal and a protein containing meal prevented the inactivation of lipase of the duodenal juice and most of the pancreatin

preparates examined. Furthermore, some mg of soybean trypsin inhibitor significantly enhanced the effectiveness of crumbled Panpur tablets which were without effect on the steatorrhea of the same patients in the enteric coated tablet form. Amylase proved to be stable; some auto-inactivation of trypsin was demonstrated at a later phase. It has been proposed that proteolytic inactivation of lipase can be prevented by increasing the lipase-trypsin ratio to physiological levels and by the amelioration of mixing the pancreatin with protein containing meals [51, 53]. The recently developed pancreatin preparations work better although these requirements are not sufficient (Figure 1).

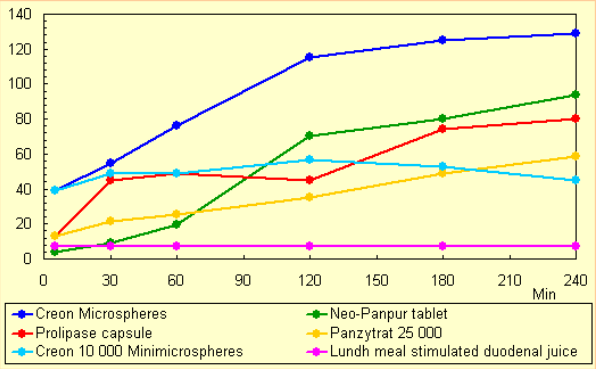

Figure 1. Lipase-trypsin ratio.

In vivo studies in humans using non-absorbable markers have demonstrated that 74% of amylase, 22% of trypsin and only 1% of lipase delivered to the duodenum survived transit to the ileum [54]. In vitro triolein and bile acids had some protective effect on lipolytic activity [55]. The proteolytic inactivation of lipase and colipase can be also prevented by proteins giving alternative substrates for proteases [51, 53, 55]. The protective effect of triglycerides requires colipase to form a substrate-colipase-lipase complex for fat digestion mainly in the presence of bile.

In patients with alcoholic chronic pancreatitis, the ratio of protease to lipase activity is high in the duodenal juice because of trypsin and chymotrypsin prevalent in pancreatic secretion. Proteolytic inactivation of lipase in these patients is more important than in normal pancreatitis. Treating them with pancreatic supplements containing a high proportion of proteases may contribute to an even faster inactivation of lipase [51, 53, 56] and to the often-noted difficulty of correcting steatorrhea [47-54]. In addition, the orthodox clinical dogma about the high carbohydrate, low protein and fat containing diet advised for chronic pancreatitis patients may further aggravate lipase survival. Although relapsing pancreatitis with pain may indicate restrictions in fat intake, medium-chain triglycerides which are particularly suitable substrates for lingual lipase [57] and can absorb less stimulating pancreatic secretion even without digestion could successfully substitute long-chain triglycerides in dietetic treatment of chronic pancreatitis. Other phospholipid and cholesterol containing meals (brain, egg yolk, liver) using carboxylester lipase and phospholipase A2 for digestion may also contribute to the survival of pancreatic lipase by ameliorating the formation of the micellar phase [57].

Ingestion of pancreatic supplements with increased proteolytic activity was proposed to diminish the pain of chronic pancreatitis by suppressing pancreatic secretion via a duodenopancreatic feedback mechanism [58]. This treatment which proved to be effective only in patients with mild to moderate pancreatic insufficiency [58] might produce steatorrhea in severe insufficiency by diminishing the survival of lipase [56] as well as by blocking the trophic effect [12, 13] of CCK release and/or the cholinergic mechanism involved in the duodenopancreatic feedback regulation. Individual administration of high lipase or high protease containing pancreatin preparations adapted to the degree of pancreatic insufficiency and to the different meals in a galenic form which allows fast mixing and segregation of proteases and lipase to their substrate could ameliorate substitution therapy in pancreatic insufficiency.

In patients with diabetic pancreatitis, the level of insulin is as important for proportionate enzyme synthesis and secretion of acinar cells as for prevention of diabetic disturbances and complications. Spiking blood sugar levels or

reactive hypoglycemia must be avoided by equilibrated carbohydrate intake and individualized, through insulin treatment if required.

Key words Celiac Plexus; Clinical Protocols; Endoscopy, Digestive System; Recovery of Function; Lithotripsy; Nutrition Disorders; Pain; Pancreatic Disease; Pancreatic Extracts; Sphincterotomy, Endoscopic

Abbreviations ESWL: extracorporeal shock wave lithotripsy; PCPB: percutaneous celiac plexus block

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