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Pancreatic Fibrosis Correlates with Exocrine Pancreatic Insufficiency after Pancreatoduodenectomy

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Key Words
Exocrine-endocrine pancreatic function · Pancreatoduodenectomy · Pancreatic fibrosis

Abstract
Background: Obstruction of the pancreatic duct can lead to pancreatic fibrosis. We investigated the correlation between the extent of pancreatic fibrosis and the postoperative exocrine and endocrine pancreatic function. ***Methods:*** Fifty-five patients who were treated for pancreatic and periampullary carcinoma and 19 patients with chronic pancreatitis were evaluated. Exocrine pancreatic function was evaluated by fecal elastase-1 test, while endocrine pancreatic function was assessed by plasma glucose level. The extent of fibrosis, duct dilation and endocrine tissue loss was examined histopathologically. ***Results:*** A strong correlation was found between pancreatic fibrosis and elastase-1 level less than 100 μg/g ($p < 0.0001$), reflecting severe exocrine pancreatic insufficiency. A strong correlation was found between pancreatic fibrosis and endocrine tissue loss ($p < 0.0001$). Neither pancreatic fibrosis nor endocrine tissue loss were correlated with the development of postoperative diabetes mellitus. Duct dilation alone was neither correlated with exocrine nor with endocrine function loss. ***Conclusion:*** The majority of patients develop severe exocrine pancreatic insufficiency after pancreatoduodenectomy. The extent of exocrine pancreatic insufficiency is strongly correlated with preoperative fibrosis. The loss of endocrine tissue does not correlate with postoperative diabetes mellitus. Preoperative dilation of the pancreatic duct per se does not predict exocrine or endocrine pancreatic insufficiency postoperatively.

Introduction

Both pylorus-preserving pancreatoduodenectomy and the classic Whipple resection are nowadays standard procedures for various benign and malignant diseases in the periampullary region. The morbidity, mortality and long-term survival after resection have been reported to be comparable for both procedures [1–4].

Advances in operative techniques and improvements in perioperative management have led to an increasing number of long-term survivors after resection [5]. Therefore, their functional outcomes have attracted more attention. Exocrine and endocrine pancreatic functions seem to be affected by factors such as the type of pancreatoenterostomy, the preoperative condition of the pan-

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creas and the volume of the resected pancreas. However, the real pathogenesis behind pancreatic function loss remains unclear. From a clinical point of view, the late postoperative period is frequently characterized by various gastrointestinal problems, such as weight loss, malabsorption of essential nutrients (for example, fat-soluble vitamins) and steatorrhea, due to malfunctioning of the pancreatic remnant. Furthermore, we observed an interesting fact that even in patients with a relatively normal pancreatic remnant, exocrine insufficiency occurs at the time of operation. Moreover, a substantial part of the patients develop diabetes mellitus after pancreatoduodenectomy. Fibrosis of the parenchyma of the pancreas has never been investigated before as a factor contributing to the malfunction of the pancreatic remnant.

Therefore, we hypothesized that fibrosis of the pancreatic remnant secondary to chronic pancreatic duct obstruction might contribute to these functional changes of the pancreas.

The aim of this study was to assess the correlation between the preoperative changes of the pancreas parenchyma (as reflected by the dilation of the pancreatic duct and the extent of fibrosis at the plane of transection) and the postoperative exocrine and endocrine function at least 6 months after pancreatoduodenectomy.

Patients and Methods

Clinical Characteristics

In 2006, a nonconsecutive series of 55 patients, who had undergone pancreatoduodenectomy for either pancreatic or periampullary cancer at the Erasmus Medical Center in Rotterdam (The Netherlands) between 2001 and 2005, were evaluated for this clinical study. Thirty-two patients had been treated for pancreatic cancer and 23 for periampullary cancer. Periampullary cancer was defined as cancer of the papilla vateri, distal bile duct cancer or periampullary duodenal cancer; pancreatic cancer was defined as cancer elsewhere in the pancreatic parenchyma. In addition, 19 patients with chronic pancreatitis who underwent pancreatoduodenectomy during the same period were studied.

Patients were evaluated in the outpatient clinic, where they were seen as a consecutive group for follow-up. Patients had to be at least 6 months after operation without signs of tumor recurrence and their resection specimen had to be available for careful examination.

There were 45 men and 29 women. The mean age of these patients was 58.5 years (range 20–83).

Surgery

After exclusion of distant metastasis and local irresectability, all patients underwent pancreatoduodenectomy. Twenty-six patients had a classical Kausch-Whipple resection, whereas 48 patients underwent pylorus-preserving pancreatoduodenectomy. End-to-side double-layer duct-to-mucosa pancreatojejunostomy was made according to the technique described by Cattell [6]. Subsequently, single-layer end-to-side hepaticojejunostomy was performed. Finally antecolic end-to-side anastomosis was made between either the proximal duodenum or the gastric remnant and the proximal jejunum.

Exocrine Function Assessment

To assess exocrine pancreatic function, the fecal elastase-1 test was used. Two feces samples were collected from each patient at least 6 months postoperatively. In 20 patients, preoperative elastase-1 concentration was also available. The elastase-1 concentration was measured with a commercially available ELISA kit (Schebo Biotech AG, Giessen, Germany). Enzyme replacement therapy was continued during the test period, since this does not affect the test results [7].

Pancreatic function was considered normal when fecal elastase-1 concentration exceeded 200 μg/g feces, moderately insufficient when fecal elastase-1 concentration was between 100 and 200 μg/g feces and severely insufficient when elastase-1 concentration was less than 100 μg/g feces.

Endocrine Function Assessment

Before surgery, apart from a casual glucose and hemoglobin glucose level determination, patients were asked whether they suffered from diabetes mellitus, polydipsia or polyuria and whether they used insulin or oral antidiabetic medication. During follow-up, casual glucose levels were measured frequently and patients were asked the same questions.

Histology

The use of a semiquantitative method (the subjective quantification of an experienced individual pathologist) in the assessment of histological changes of parenchyma, such as fibrosis, is considered accurate.

In order to score the atrophy of the pancreas, an experienced gastrointestinal pathologist (H.v.D.) examined the plane of resection through the pancreas. Serial cross-sections of the plane of resection were fixed in 20% neutral phosphate-buffered formalin for light microscopy. Paraffin sections were stained with hematoxylin and eosin. The extent of fibrosis and remaining functional exocrine tissue were assessed using a semiquantitative measurement method with 20-fold enlargement for light microscopy. Abnormalities were classified as mild or not affected if less than 25% fibrosis was observed, moderate if there was 25–75% and severe if more than 75% fibrosis was present (fig. 1). Furthermore, the extent of dilation of the pancreatic duct was assessed. Dilation was defined as a duct diameter of more than 2 mm. In patients with missing histological duct samples, operation reports and radiological data were screened for signs of duct dilation.

Endocrine tissue loss was determined in the plane of resection through the pancreas. Because of the more spread distribution of islands of Langerhans in the pancreatic corpus/tail, the presence of endocrine tissue was scored in only 2 categories semiquantitatively, that is, as mild when the estimated loss of endocrine tissue in the parenchyma was less than 50% compared with a normal pancreas parenchyma or as severe when the estimated loss of endocrine tissue was more than 50%.

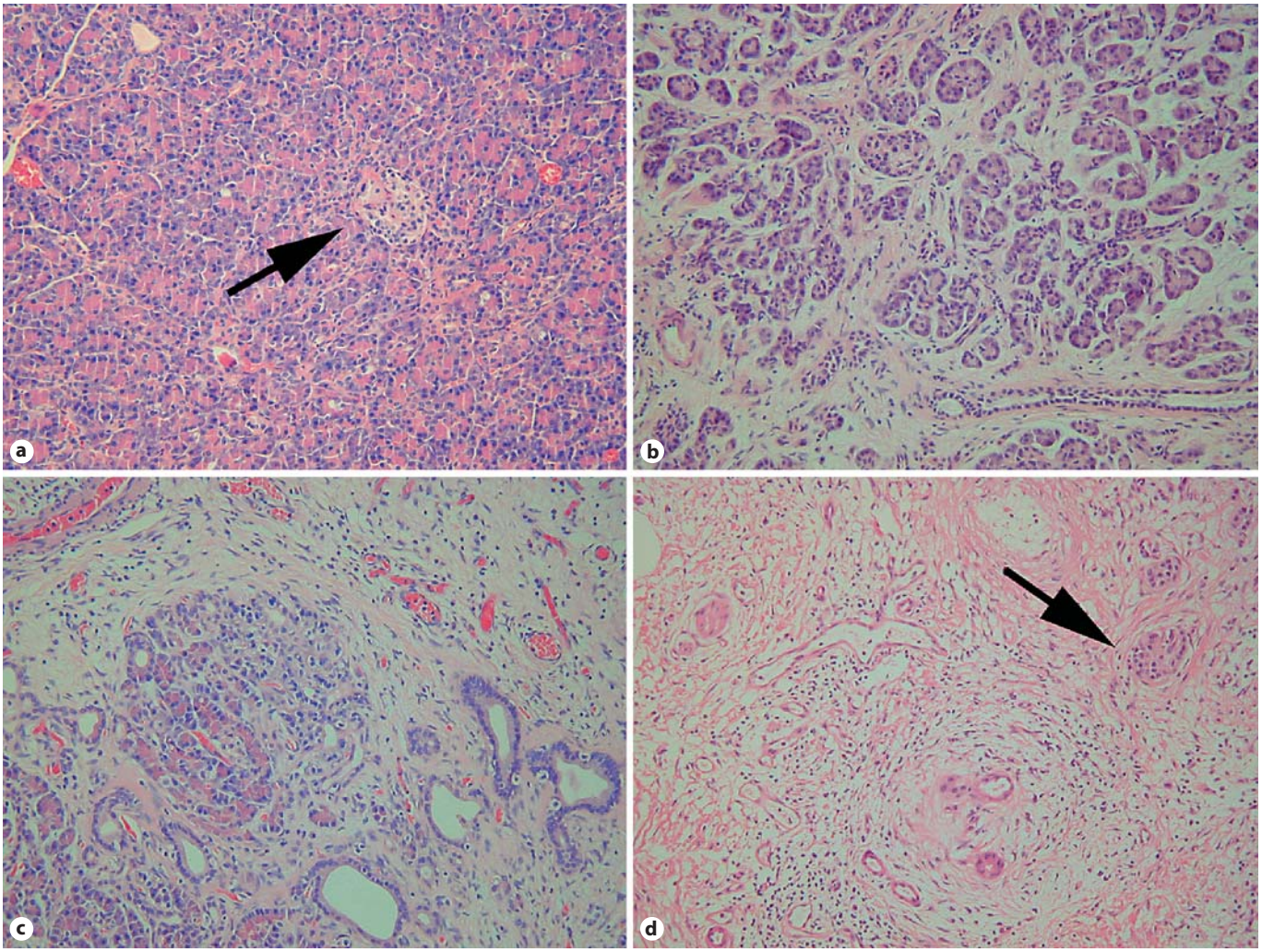

Fig. 1. Histopathological classification of pancreatic fibrosis. **a** Normal pancreatic parenchyma with normal distribution of exocrine and endocrine tissue (arrow indicates Langerhans islet). **b** Mild fibrosis. **c** Moderate fibrosis. **d** Severe fibrosis (arrow indicates Langerhans islet).

Statistics

Data were analyzed using SPSS® version 11.0 (SPSS Inc., Chicago, Ill., USA). The Mann-Whitney U test was performed for assessing the study population means. Spearman's rank test was used to determine correlations. The one-way ANOVA test was used to compare means of different groups, post hoc tested with the Bonferroni test. Test results were considered to denote statistical significance if $p < 0.05$.

Results

Elastase-1

Of the 74 patients, 56 (76%) showed fecal elastase-1 levels less than 100 μg/g, indicating severe pancreatic insufficiency. Nine patients had elastase-1 levels between 100 and 200 μg/g, indicating mild insufficiency, and only 9 patients had elastase levels above 200 μg/g, which indicates a normally functioning remnant.

There was no significant difference in distribution of exocrine insufficiency in the 3 distinct groups as identified by underlying disease: severe insufficiency was found in 28/32 patients (88%) with pancreatic cancer, in 13/23 patients (57%) with periampullary cancer and in 15/19 patients (79%) with chronic pancreatitis.

In the 20 patients in whom both pre- and postoperative elastase-1 levels were available, there was a significant decline postoperatively ($p < 0.02$; fig. 2).

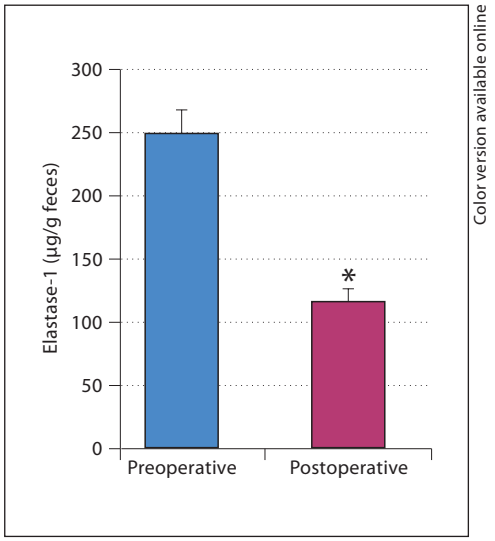

Fig. 2. Preoperative and postoperative elastase-1 concentration in 20 patients who underwent pancreatoduodenectomy. * p = 0.02.

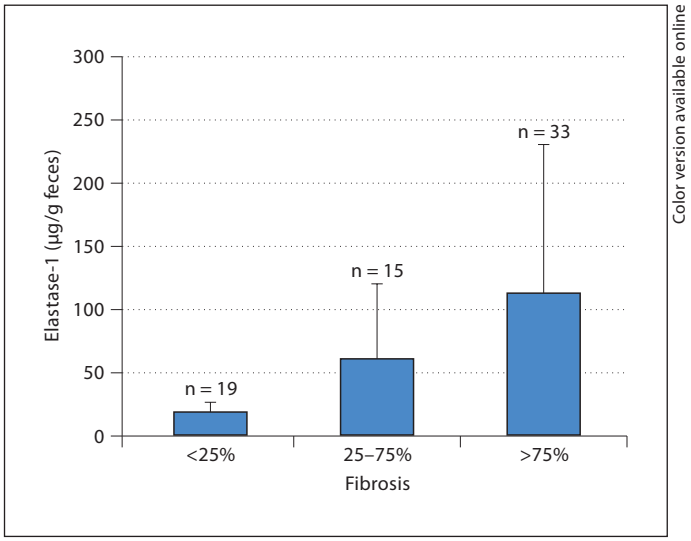

Fig. 3. Inversed correlation between the extent of fibrosis and elastase-1 level. p < 0.0001.

Fibrosis

In 7 patients, no histological examination could be performed because of missing samples. Of the remaining 67 patients, 33 had mild, 15 moderate and 19 severe fibrosis. The distribution of the extent of fibrosis between the groups with different underlying disease is shown in table 1; there was no significant difference between the groups (p = 0.08). A strong inverse correlation was observed between the extent of fibrosis and the level of elastase-1 in the fecal samples, both reflecting exocrine tissue loss (p < 0.0001; fig. 3).

Duct Dilation

In 2 patients, no data could be retrieved to assess pancreatic duct diameter. The extent of pancreatic duct dilation in the groups with different underlying diseases is outlined in table 1; no significant difference was found between the 3 groups (p = 0.162). There was no (inversed) correlation between a dilated pancreatic duct and elastase-1 levels in the feces (p = 0.599) or extent of fibrosis in the resection plane (p = 0.464).

Endocrine Tissue

The loss of endocrine tissue in the resection plane could not be assessed in 7 patients because of missing samples. The results of endocrine tissue assessment are shown in table 1. Again, there were no significant differences between the groups (p < 0.838). A strong correlation existed between endocrine tissue loss and the extent of fibrosis (p < 0.0001). No correlation existed between endocrine tissue loss and pancreatic duct dilation (p = 0.735).

Diabetes Mellitus

There were no missing samples. Sixty-four patients did not have diabetes before the operation. Prior to surgery, 6 patients were already diagnosed as having insulin-dependent diabetes and 4 patients were on oral antidiabetic medication. Overall, 19 patients (26%) developed diabetes after the operation (13 insulin-dependent diabetes, 6 non-insulin-dependent diabetes). Neither for pancreatic duct dilation (p = 0.543) nor for endocrine tissue loss (p = 0.521) could a correlation be identified with postoperative diabetes (with or without preoperative diabetes).

Discussion

This study focuses on the postoperative pancreatic function and its relation with preoperative loss of exocrine and endocrine pancreatic tissue (fibrosis) and a dilated pancreatic duct. Pancreatic function can be altered during the course of chronic pancreatitis. The main reasons for the development of insufficiency are fibrosis and loss of functional tissue. In pancreatic cancer, especially the periampullary cancers, the destruction by cancer tissue can be comprehended, but the remaining tissue is supposed to be sufficient and normal.

Table 1. Distribution of histological and hormonal changes in patients with pancreatic carcinoma, periampullary carcinoma and chronic pancreatitis

Fibrosis	Unknown	Mild (<25%)	Moderate (25–75%)	Severe (>75%)	Total
Pancreatic carcinoma	3	12	5	12	32
Periampullary carcinoma	4	15	4	0	23
Chronic pancreatitis	0	6	6	7	19
Total	7	33	15	19	74
Pancreatic duct dilation	**Unknown**	**No duct dilation**		**Duct dilation**	**Total**
Pancreatic carcinoma	0	4		28	32
Periampullary carcinoma	1	4		18	23
Chronic pancreatitis	1	7		11	19
Total	2	15		57	74
Endocrine tissue (% Langerhans islets)	**Unknown**	**Low (0–50%)**		**High (50–100%)**	**Total**
Pancreatic carcinoma	3	14		15	32
Periampullary carcinoma	4	1		18	23
Chronic pancreatitis	0	9		10	19
Total	7	24		43	74
Diabetes mellitus	**None**	**Preoperative**		**Postoperative**	**Total**
Pancreatic carcinoma	20	5		7	32
Periampullary carcinoma	14	3		6	23
Chronic pancreatitis	11	2		6	19
Total	45	10		19	74

The majority of patients showed postoperative fecal elastase-1 levels lower than 100 μg/g, indicating severe exocrine pancreatic insufficiency. Pancreatoduodenectomy is associated with exocrine and endocrine alterations [8–11]. During follow-up, patients frequently report difficulties with food intake, periods of diarrhea, altered consistency of feces, steatorrhea and symptoms of malabsorption and subsequent malnutrition [12]. Huang et al. [13] reported a prevalence of 47 and 59% for foul stool after pancreatoduodenectomy because of malignant or benign pathology respectively, as well as 41 and 39% diabetes, respectively, in a population of 192 patients. In another study, exocrine insufficiency symptoms like gross steatorrhea increased from 17% before to 43% after surgery [14].

Exocrine insufficiency can be tested by direct or indirect function tests. The direct tests are more time-consuming, more expensive and unpleasant for the patients. Indirect tests, such as the fecal elastase-1 test, measure the consequences of pancreatic insufficiency and are more widely available.

The elastase-1 test was used because of the good results obtained in previous studies in assessing moderate to severe exocrine dysfunction of the pancreas [7, 15–20]. This test has several advantages. First of all, the enzyme is stable during intestinal transport, secondly, elastase is concentrated in the feces, and finally, the enzyme is easily detected by means of an ELISA test.

Pancreatic atrophy and concomitant fibrosis are thought to be responsible for the loss of exocrine and endocrine function [21]. Occlusion of the pancreatic duct by tumor, by chronic inflammation coexisting with tumor or merely by chronic pancreatitis, causes fibrosis of the parenchyma [22–25]. In this study, a significant inversed correlation was found between the histopathological extent of fibrosis and the level of elastase-1 test in the feces.

Tanaka et al. [24] reported an improvement of exocrine pancreatic function after 1 year compared with the test results within 2 months postoperatively. We did not analyze this phenomenon, since we only investigated patients more than 6 months postoperatively. In contrast to

data from the literature, no inversed correlation was found between a dilated pancreatic duct and postoperative elastase-1 levels in the feces (p = 0.599). Dilation of the pancreatic duct was neither correlated with exocrine nor with endocrine tissue loss. Therefore, a dilated pancreatic duct may be a sign of serious disease, but not a parameter of tissue destruction. Sato et al. [23] mentioned a short-term postoperative exocrine impairment in patients with a preoperatively dilated pancreatic duct. Interestingly, a substantial number of patients in our study with a normal pancreatic duct at the time of operation and only mild fibrosis still developed a severe exocrine insufficiency postoperatively, which suggests an ongoing exocrine and endocrine tissue loss after pancreatoduodenectomy. Pancreatic atrophy, as assessed by subtracting the diameter of the pancreatic duct from the total gland thickness, has previously been shown to develop over time following pancreatoduodenectomy [26] and to correlate well with exocrine insufficiency. Partial or total obstruction of the anastomosis might explain this phenomenon in some of the patients. Even a duct-to-mucosa anastomosis (which we also performed in all patients) could not prevent the ongoing process of tissue destruction in that study. It has been suggested that a pancreatojejunostomy allows a better preservation of the pancreatic exocrine function than a pancreatogastrostomy, which may be explained at least partly by neutralization of pancreatic enzymatic secretions due to gastric acid.

In our study, a strong correlation existed between endocrine tissue loss and the extent of fibrosis, but there was no correlation between endocrine tissue loss and pancreatic duct dilation. Strikingly, neither pancreatic duct dilation nor endocrine tissue loss were correlated with postoperative diabetes mellitus. Since pancreatic fibrosis and exocrine tissue loss were studied 6 months before the clinical endocrine and exocrine study, the observation that endocrine tissue loss is not correlated with diabetes mellitus could be explained by the persistence of endocrine tissue loss after the operation. This could also explain the fact that not all patients known with diabetes mellitus after 6 months were diabetic directly postoperatively.

In a recent review, 70% of patients with pancreatic carcinoma had an impaired glucose tolerance test or frank diabetes preoperatively [27]. Some authors suggest that diabetes may be an early manifestation of pancreatic malignancies [10, 28]. Jang et al. [29] reported an onset of diabetes mellitus in 44% of patients after pancreatoduodenectomy with pancreatojejunostomy and even in 75% after pancreatoduodenectomy with pancreatogastrostomy. Sakorafas et al. [14] reported an increase in diabetes from 8% before to 48% after pancreatoduodenectomy for chronic pancreatitis.

In pancreatic head resection, 30–50% of the pancreatic parenchyma is involved and thus some degree of pancreatic insufficiency is induced [30, 31]. Taking into account that most of the Langerhans islets are located in the tail of the pancreas, which is left in situ during pancreatoduodenectomy [26], the frequent postoperative onset of diabetes is less easy to explain. It has been suggested that other mechanisms are involved, such as an ongoing atrophy of the pancreatic parenchyma with impairment of the function of the islets of Langerhans. The loss of insulin-secreting capacity was clearly shown in experimental data with dogs after pancreatic duct obstruction [25]. Clinical data from our group showed that iatrogenic pancreatic duct occlusion after pancreatoduodenectomy leads to a significantly higher risk of endocrine insufficiency [32].

More than one quarter of the patients developed diabetes after the operation, while 1 of 7 had diabetes already preoperatively. The decline of glucose tolerance after pancreatoduodenectomy seems to be associated with a low reserve of endocrine function rather than with the choice of a specific anastomosis (pancreaticojejunostomy or pancreaticogastrostomy) with its related complications [33].

Our study has several limitations. Since the study population consisted of a nonconsecutive series of patients who were enrolled over a relatively long study period, an unintended patient selection bias might have played a role. However, as with other studies of pancreatic cancer, many patients died before enrollment, developed recurrent disease or were lost to follow-up. As the aim of this study was to assess the correlation between the preoperative changes of the pancreas parenchyma and the postoperative exocrine and endocrine function at least 6 months after pancreatoduodenectomy, we did not mean to measure the elastase-1 concentration preoperatively. The results of elastase-1 concentration were notably abnormal during the study period and for this reason we decided to measure the elastase-1 concentration also in the preoperative phase in order to compare. This could be obtained from a small number of patients (n = 20). Another criticism might be the relatively small number of patients in this study, which induces the risk of type 2 statistical errors. The study objectives were merely aimed at the clinical signs and feasibility of quantification of a histological observation. Since the results were obvious, we concluded that it was not necessary to extend the number of patients.

Furthermore, a later time point would have given more information about the course of the exocrine and endocrine insufficiency. Because the long-term survivors after a pancreatoduodenectomy do not seem to improve over years, the quality of life aspects become more important and therefore improvements in the clinical conditions must be pursued.

Finally, the semiquantitative histopathological analysis might be a relatively inaccurate method to judge the loss of exocrine and endocrine tissue.

In conclusion, after pancreatoduodenectomy, the extent of exocrine pancreatic insufficiency is strongly correlated with preoperative fibrosis reflecting the preoperative loss of functional pancreatic tissue. However, the loss of endocrine tissue does not correlate with postoperative diabetes mellitus. Preoperative dilation of the pancreatic duct per se does not predict exocrine or endocrine pancreatic insufficiency postoperatively.

The high frequency of both exocrine and endocrine insufficiency after pancreatoduodenectomy warrants careful enzymatic supplementation and hormonal regulation during postoperative follow-up.

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