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The impact of pancreaticoduodenectomy on endocrine and exocrine pancreatic function: A prospective cohort study based on pre- and postoperative function tests.

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Running title: Evolution of pancreatic function

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Abstract**Background / Objectives:**

Studies reporting on function after pancreatic surgery are frequently based on diabetes history, fasting glycemia or random glycemia. The aim of this study was to investigate prospectively the evolution of pancreatic function in patients undergoing pancreaticoduodenectomy based on proper pre- and postoperative function tests. It was hypothesised that pancreatic function deteriorates after pancreaticoduodenectomy.

Methods:

Between 2013-2016, 78 patients undergoing pancreaticoduodenectomy for oncologic indications had a prospective evaluation of their endocrine and exocrine pancreatic function. Endocrine function was evaluated with the 75 g oral glucose tolerance test (OGTT) and the 1 mg intravenous glucagon test. Exocrine function was evaluated with a ¹³C-labelled mixed-triglyceride breath test. Tests were performed pre- and postoperatively.

Results:

In 90.5 % (19/21) of patients with preoperatively known diabetes, no change in endocrine function was observed. In contrast, endocrine function improved in 68.1 % (15/22) of patients with newly diagnosed diabetes. 40 % (14/35) of patients with a preoperative normal OGTT or prediabetes experienced deterioration in function. In multivariate analysis, improvement of newly diagnosed diabetes was correlated with preoperative bilirubin levels ($p=0.045$), while progression towards diabetes was correlated with preoperative C-peptidogenic index T_{30} ($p=0.037$).

A total of 20.5 % (16/78) of patients had pancreatic exocrine insufficiency preoperatively. Another 51.3 % (40/78) of patients deteriorated on exocrine level. In total, 64.1 % (50/78) of patients required pancreatic enzyme-replacement therapy postoperatively.

Conclusions:

Although deterioration of endocrine function was expected after pancreatic resection, improvement is frequently observed in patients with newly diagnosed diabetes. Exocrine function deteriorates after pancreaticoduodenectomy.

Main Text

Introduction

Since pancreaticoduodenectomy or PD implies the resection of a part of the functional pancreatic parenchyma, it was hypothesised that pancreatic function would deteriorate following resection of a pancreatic head tumour.

Following pancreaticoduodenectomy, however, the resolution of diabetes mellitus has also been reported¹⁻³, the diabetes resolution rate ranges from 30.5 to 65%. There has been no in-depth study of factors explaining and contributing to this resolution of diabetes.

Studies reporting on the evolution of pancreatic function after pancreatic surgery are frequently based on poor preoperative evaluation of the pancreatic function: history of diabetes, fasting glycemia or random glycemia⁴⁻¹⁰. In the present study the added value lies in the proper preoperative evaluation of the endocrine and exocrine function as a reference point for postoperative function tests.

Several authors have reported on factors predicting and influencing postoperative endocrine function.

Yoshikawa *et al.*¹¹ reported on parenchymal thickness as a parameter for predicting postoperative insulin secretion. Hirata *et al.*¹² found that body mass index above 25 and hard pancreatic texture are independent risk factors for new-onset diabetes after pancreaticoduodenectomy. Nagino *et al.*¹³ reported on the influence of obstructive jaundice on glucose metabolism. In the literature, the value of multiple OGTT-based beta-cell function indices and scores has been studied as a predictive tool for developing diabetes and prediabetes in a general population^{14, 15}. It would be interesting to look for these relations in the patient population under study: patients who have to undergo pancreaticoduodenectomy.

Some authors¹⁶ have also reported on the interactions between endocrine and exocrine function. When exocrine function fails, deterioration in endocrine function will follow. Progressive fibrosis, a result from pancreatic cancer by activation of the pancreatic stellate cells, also reduces the beta-cell mass. With the destruction of the endocrine tissue, insulin secretion is progressively reduced and the glucose tolerance is impaired. The evolution of the exocrine function after pancreaticoduodenectomy and its possible consequences for the endocrine function was therefore included in this study. Also the possible atrophy of the pancreatic remnant due to a pancreatic head tumor has been assessed on imaging.

Methods

Patient recruitment and data collection

During the period 2013 to 2016, a total of 78 patients undergoing pancreaticoduodenectomy for oncologic indications were enrolled in a prospective cohort study evaluating the endocrine and exocrine pancreatic function before and after surgery. Patients undergoing surgery for chronic pancreatitis, or benign but functional neuroendocrine tumours, were excluded. Patients undergoing PD for oncologic indications, but not showing up for follow-up examinations, were also excluded from the analysis due to lack of data.

The endocrine pancreatic function was evaluated with a 75 g OGTT (Glucomedics®, Lambra) and 1 mg intravenous (IV) glucagon test (Glucagen Hypokit®, Novonordisk Pharma). In patients with a known history of diabetes and treated with oral antidiabetic medication or insulin therapy (categorized as 'known diabetes'), only the 1 mg intravenous glucagon test was performed. During the OGTT, after ingestion of 75 g of glucose, blood samples were taken at 0, 30, 60 and 120 minutes for the determination of glycated haemoglobin (%), glycaemia (mg/dl), insulin (pmol/l) and C-peptide (nmol/l) levels. During the glucagon test, following the intravenous injection of 1 mg glucagon, blood samples were procured at 0 and 6 minutes for the determination of glycaemia, insulin and C-peptide levels.

Patients with a known history of diabetes at the moment of surgical intake and/or treated with medication for this disease, were classified as 'known diabetes'. Patients who underwent OGTT and had, based on this test, a new diagnosis of diabetes according to American Diabetes Association (ADA) criteria, were classified as 'newly diagnosed' diabetes.

The exocrine pancreatic function was tested with a ¹³C-labelled mixed-triglyceride (MTG) breath test. During the breath test, 250 mg of the substrate 1,3-distearyl-(¹³C-Carboxyl)octanol glycerol was mixed with a test meal and digested in the small bowel through lipase. The breath test analyses the cumulative recovery of ¹³-CO₂ (cumulative dose percentage) with isotope ratio mass spectrometry. There is an excellent correlation between bowel lipase activity and ¹³-CO₂ concentrations in the breath. Exocrine insufficiency is associated with low cumulative-dose % ¹³-CO₂ recovery in this breath test^{17, 18}.

These tests were performed in the days before the scheduled pancreaticoduodenectomy and four to six weeks after surgery. Special attention was given to the performance of the postoperative test before eventual

chemotherapy was initiated, since chemotherapy regimens usually involve corticoid administration, which can obviously influence the endocrine function.

Patients most frequently underwent a pylorus-preserving pancreaticoduodenectomy with standard lymphadenectomy¹⁹, no extended resections were included. The pancreatic neck was divided over the anterior surface of the portal vein. Immediate postoperative feeding regimen was enteral nutrition by nasojejunal tube.

Definition of (sub)groups according to the evolution of pancreatic endocrine function

The ADA criteria²⁰ were used to interpret the endocrine function. Following interpretation of the preoperative OGTT and glucagon test results, patients were categorised into three groups according to their endocrine function: 1/ diabetic patients with a history of diabetes known at the moment of surgical intake or confronted with a new diagnosis of diabetes according to their preoperative OGTT; 2/ patients with prediabetes: impaired fasting glucose levels (IFG), impaired glucose tolerance (IGT) or both; and 3/ patients with a normal OGTT.

Patients who did not require oral antidiabetic medication or insulin therapy postoperatively underwent OGTT and IV glucagon testing again and were recategorised according to these results. Patients were classified as non-progressors (NP) if the endocrine function remained stable after surgery, while patients in the same functional category were classified as progressors (P) if the endocrine function deteriorated, and as improvers (I) if they evolved towards resolution of diabetes.

Factors predicting the functional evolution

To explain and predict this evolution of the endocrine function following pancreaticoduodenectomy, several factors with a possible causal correlation were evaluated (Table 1).

Weight and height were measured by a qualified nurse before and after surgery, and body mass index (BMI) was calculated. In the postoperative follow up, these parameters were reassessed at the same moment when the postoperative MTG breath test was performed (4-6 weeks after surgery).

Patients undergoing surgery for pancreatic head tumours are frequently confronted with a certain degree of parenchymal atrophy in the pancreatic remnant. To determine this atrophy, the main pancreatic duct diameter and parenchymal diameter were measured on preoperative imaging (preferably MRI, otherwise multiphase CT-scan) as previously described by Yoshikawa¹¹. All the measurement were performed by the same physician to

rule out interobserver variability. Preoperative measurement of the main pancreatic duct size (measured by probes) and parenchymal consistency were noted by the surgeon. A main pancreatic duct was considered dilated > 3mm.

Since jaundice could impair insulin secretion, hepatic insulin extraction and glucose metabolism, preoperative levels of bilirubin and eventual bile duct drainage by ERCP or trans-hepatic biliary catheter were scored ¹³.

Beta-cell function and insulin sensitivity and resistance (HOMA2-%B, HOMA2-%IS and HOMA2-IR respectively) were assessed using HOMA2 (homeostasis model assessment 2) index calculations through the computer application provided by the Oxford Centre for Diabetes, Endocrinology and Metabolism ^{21, 22}, based on fasting plasma glucose and C-peptide levels.

Many other OGTT-based beta-cell function indices for the prediction of prediabetes or diabetes have been calculated and are listed in Table 1 ¹⁴.

Ethical considerations

Both informed consent and the approval of the local Ethical Committee were acquired (Belgian registration number: BE300201318590). This study was conducted according to the ethical principles stated in the 'Declaration of Helsinki' and in 'Good Clinical Practice'.

Statistical analysis

Results were analysed using SPSS (version 23.0, Chicago, IL), with data expressed as means (standard deviation) for normally distributed continuous variables and medians (range) for non-normally distributed continuous variables. Categorical data are expressed as numbers (%). The normal distribution of continuous variables was assessed using the Shapiro-Wilk method. To compare medians for polychotomous outcome parameters, the Kruskal-Wallis method for non-normally distributed variables was used. To compare paired non-normally distributed variables before and after surgery, the Wilcoxon signed rank test was used. A two-tailed P-value < 0.05 was considered significant. Stepwise forward logistic regression analysis was done to assess the strength and independency of correlations. Only parameters with $p < 0.1$ were taken into account for multivariate analysis.

Results

Seventy-eight patients were enrolled in this prospective cohort study. Patient characteristics are outlined in Table 2. Median age at the time of surgery was 66 years (range 38-86 years). A total of 75.6 % (59/78) of patients underwent pancreaticoduodenectomy for an adenocarcinoma at the pancreatic head, but oncologic pancreatic head resection was also performed for premalignant lesions such as intraductal papillary mucinous neoplasia or mucinous cysts (5.1 % or 4/78) and neuroendocrine tumours larger than 2 cm (7.7 % or 6/78). A total of 11.5 % (9/78) of patients underwent PD for imaging suspect for malignancy, but a malignant lesion could not be confirmed in the resection specimen.

Based on preoperative endocrine function tests and history, 26.9 % (21/78) of patients had known diabetes treated with oral antidiabetic medication or insulin therapy, while 28.2 % (22/78) were, according to ADA criteria²⁰, newly diagnosed with diabetes. A total of 28.2 % (22/78) had prediabetes: impaired fasting glycaemia, impaired glucose tolerance or both, and another 16.6 % (13/78) had a normal glucose metabolism (Figure 1).

Preoperative pancreatic exocrine insufficiency evaluated with the MTG breath test was present in 20.5 % (16/78) of patients (Figure 1).

Endocrine function tests after pancreaticoduodenectomy (Figure 1) revealed that 53.8 % (42/78) of patients did not experience any change in endocrine function (non-progressors), while in 28.2 % (22/78) the function did improve (improvers) and in 17.9 % (14/78) it deteriorated (progressors). A total of 90.5 % (19/21) of patients with known diabetes and 50 % (11/22) of patients with prediabetes did not experience any change in function and remained diabetic or prediabetic. On the other hand, in 68.1 % (15/22) of patients with preoperative newly diagnosed diabetes, function did improve after surgery (11 patients evolved towards prediabetes, while four even had total resolution of the diabetes). A total of 9.5 % (2/21) of patients with known diabetes evolved towards prediabetes, while 22.7 % (5/22) of patients with preoperative prediabetes experienced normalisation of the OGTT.

Exocrine function tests revealed that 51.3 % (40/78) of patients experienced deterioration of the exocrine function, whereas preoperatively 20.5 % (16/78) already had pancreatic exocrine insufficiency (Figure 1). A total of 25 % (4/16) of patients with a preoperative low MTG breath test experienced improvement after resection. Following resection, 64.1 % (50/78) of patients had pancreatic exocrine insufficiency (PEI) and a

need for enzyme replacement therapy based on the MTG breath test. In patients with a preoperative normal MTG: median cumulative recovery, the percentage decreased from 37.5 % (range: 23.7-121.4%) preoperatively to 15.4 % (range: 1.7-60.1%) postoperatively ($p<0.001$). An analysis of the evolution of the endocrine function according to their postoperative pathological examination (malignant and non- malignant lesions separately) has also been performed (Figure 2 and Table 3). There was a significantly larger proportion of progressors (38.9% or 7/18 patients) in the group of the non-malignant lesions compared with the group of malignant lesions (11.6% or 7/60) ($p=0.014$). On the other hand, there was a larger proportion of patients whose endocrine function improved from newly diagnosed diabetes in the group with malignant lesions (31.7% or 14/60) than in the group with non-malignant lesions (16.7% or 1/18). However, here was only a trend towards statistical significance ($p=0.084$). To put this finding into its right perspective, one should take into account that, although statistically not different, preoperative diabetes (known and newly diagnosed) was present in 7/18 or 39% of patients with non-malignant lesions, and in 36/60 or 60 % of patients with malignant lesions. In this series all patients who improved from newly diagnosed diabetes had malignant lesions except one.

The evolution of endocrine function before and after surgery is summarised in Table 4. An analysis of the entire group revealed that BMI, fasting serum insulin, fasting C-peptide, C-peptidogenic index T_{30} , ΔC -peptide (T_6 - T_0), HOMA2 beta-cell function and HOMA2 insulin resistance decreased significantly after surgery, while HOMA2 insulin sensitivity increased significantly.

Also of interest is the evolution of the different subgroups: in the subgroup of progressors, there is a significant decrease in C-peptidogenic index T_{30} , which is not observed in patients whose function improved or remained unchanged ($p=0.010$) (Table 4).

An analysis of the subgroup of patients preoperatively categorised as prediabetic reveals a significant difference for HOMA2 insulin sensitivity and HOMA2 insulin resistance between patients who experienced improvement in their function after surgery compared to those who did not. For HOMA2-%IS in improvers the median value was 73.6 (range: 61.9-100.3), whereas for non-improvers the median value was 53.4 (range: 26.3-92.3) ($p=0.024$). For HOMA-IR in improvers the median value was 1.37 (range: 1.00-1.62), whereas for non-improvers the median value was 1.87 (range: 1.08-3.80) ($p=0.024$). Other factors in relation to this finding, such as preoperative and postoperative BMI, Finnish Diabetes Risk Score (FINDRISC)¹⁵, weight loss after surgery and waist circumference, were not statistically different between the improver and non-improver subgroups.

In the subgroup of newly diagnosed diabetes, the improvers had a dilated main pancreatic duct at the transection site significantly more frequently (66 % or 10/15 patients) than the patients who did not improve at endocrine functional level after PD (only 14.3% or 1/7) ($p=0.021$). This was the only factor in this subgroup that was significantly different when improvers from newly diagnosed diabetes were compared with non-improvers.

In progressors, preoperative Δ C-peptide, a predictor of postoperative insulin secretion¹¹, is almost significantly different (median 0.87 nmol/l, range 0.40-1.41) compared to non-progressors and improvers (median 0.35 nmol/l, range 0.03-2.35) ($p=0.05$).

Multivariate logistic regression analysis evaluated the correlation between several parameters under study, as listed in Table 5, and the evolution of the pancreatic function. For the patients whose function deteriorated after PD, in multivariate analysis, the only factor with significant correlation was C-peptidogenic index T_{30} ($OR=31.52$ [$1.24 - 800.52$], $p=0.037$). C-peptidogenic index T_{30} as a predictor for worsened endocrine function after PD had a ROC AUC (receiver operating characteristics area under the curve) of 71.1 %. For improvers the significant factor in multivariate analysis was bilirubin at the moment of surgery ($OR=1.11$ [$1.00 - 1.23$], $p=0.045$), while ROC AUC for this factor was 62.3 %. Median bilirubin at the moment of surgery was 1.1 mg/dl (range: 0.2-24.0 mg/dl) for improvers and 0.7 mg/dl (range: 0.2-13.0 mg/dl) for patients who did not improve ($p=0.091$).

Analysing subgroups for the exocrine function, 58 patients had a normal preoperative MTG test, but the majority of these patients, 69.0 % (40/58), experienced postoperative deterioration of the exocrine function towards PEI and a need for enzyme replacement therapy. Main pancreatic duct dilatation at the transection site measured during surgery had a tendency to be more frequently associated with low postoperative MTG breath test: 65.3 % (32/49) of the patients with a dilated main pancreatic duct had a low postoperative MTG breath test compared to 40.9 % (9/22) of patients with a normal postoperative MTG breath test ($p=0.071$). Patients with a normal postoperative MTG breath test were more frequently operated on for a premalignant lesion than patients with a low postoperative MTG breath test (31.8 % or 9/22 versus 8 % or 4/50) ($p=0.028$). Multivariate analysis showed that patients operated on for a premalignant lesion are less likely to have a deteriorated postoperative exocrine function than patients operated on for a malignant lesion ($OR=0.239$ [$0.06 - 0.97$], $p=0.046$) (Table 5). Multivariate analysis of other parameters, such as pancreatic consistency, parenchymal thickness at neck or corpus, could not establish a correlation.

Discussion

Intuitively, one could expect deterioration of pancreatic function if an important part of the pancreas has to be resected for oncologic reasons. However, Pannala *et al.*¹⁰ already reported that 'having a pancreatic cancer' is a powerful diabetogenic state, that there is frequently new-onset diabetes mellitus (DM), and that DM can resolve after pancreatic resection. In their study, it resolved in 57 % of patients with new-onset DM. Several more recent papers reported varying percentages of resolution: 30.7-65 %¹⁻³. However, these reports are based on retrospective analysis and poor definition of 'diabetes mellitus' including only fasting plasma glucose and history, where in the present study, American Diabetes Association definitions²⁰ were applied, and functional tests before and after surgery were performed prospectively. Here, the percentage of resolution of DM in newly diagnosed diabetes was 68.1 % and we performed a more in-depth analysis, with calculation of most commonly used beta-cell function indices and of different factors contributing to and predicting the evolution of the endocrine and exocrine function after PD.

In the literature, a diversity of factors associated with the deterioration or improvement of pancreatic function has been identified.

One of the factors that could contribute to the diabetic state of these oncologic patients was identified by Permert *et al.* as a tumour-associated protein, namely islet amyloid polypeptide or IAPP²³⁻²⁵. This factor is involved in the development of profound insulin resistance. Although we did not measure IAPP, we observed an improvement in insulin sensitivity postoperatively, which is consistent with this idea (Table 4).

In predicting improvement or resolution of DM after PD, a correlation with several factors has been observed. Wu *et al.*³ reported that new-onset DM per se was a significant predictor, while He *et al.*² found larger and well-differentiated tumours to be associated more frequently with resolution of DM. Kang *et al.*¹ revealed PD as being more frequently associated with resolution than distal pancreatectomy. The present study confirmed the functional improvement to be more pronounced in the new-onset diabetes group, whereas the known diabetes patients barely experienced any change.

Hirata *et al.*¹² found that in diabetes patients, factors such as malignancy and long-standing DM were independent predictors for postoperatively worsened DM. In their paper, no patient with known DM or already on insulin treatment before surgery experienced improved DM after pancreatectomy. For non-diabetic patients, BMI ≥ 25 and hard pancreatic texture were independent risk factors for new-onset postoperative DM. The present study could only find a correlation between operation for a malignancy and a worsened exocrine

function, not for the endocrine function. Patients operated for a premalignant lesion were less likely to develop PEI after resection.

In the CODAM study concerning a population of 476 individuals at risk for type-2 DM and cardiovascular disease, Den Biggelaar *et al.*¹⁴ reported that insulin ratio, C-peptide ratio, insulinogenic index, C-peptidogenic index and corrected insulin response at 30 minutes²⁶ had ROC AUC over 70 % for incident type-2 diabetes. Multivariate logistic regression analysis in the present study could also identify C-peptidogenic index T_{30} as a predictor for worsened endocrine function after PD (ROC AUC is 71.1 %).

In another paper¹¹, preoperative increment of C-peptide (Δ C-peptide during IV glucagon test T_6 - T_0) and fasting plasma C-peptide are identified to be the most significant determinants of insulin secretion after PD, followed by pancreatic thickness (parenchymal diameter – diameter of main pancreatic duct). In their ROC curve, the best preoperative cut-off values for predicting the need for postoperative insulin therapy were a Δ C-peptide of 0.22 nmol/l, a fasting C-peptide of 0.28 nmol/l and a pancreatic parenchymal thickness of 6.0 mm. Although the present study found an almost significant difference in Δ C-peptide between progressors and non-progressors ($p=0.05$), we could not confirm the cut-offs predicting the need for postoperative insulin therapy.

In patients with obstructive jaundice, impaired glucose tolerance and pancreatic endocrine dysfunction due to impaired insulin secretion are frequently present – a phenomenon that is not fully reversed by drainage of the bile duct¹⁰. The liver is a key regulator of glucose metabolism and an important site for insulin extraction. Obstructive jaundice can lower insulin response to a certain glucose load. Impaired insulin secretion may require up to three months to recover after biliary drainage. This fact may explain why, in multivariate logistic regression, the only factor predicting improvement of endocrine function in this study was bilirubin level at the moment of surgery, although it was a rather weak correlation (ROC AUC was 62.3 %). This elevated bilirubin is obviously also treated by the PD itself.

In a recent review²⁷, exocrine insufficiency after pancreatectomy was present in 74 % of patients. However, most papers have not performed functional tests before and after surgery. In the present study, patients were evaluated with an MTG breath test, which has a good correlation with lipase activity in the small bowel: the accuracy rate for clinical symptoms, including clinical steatorrhea, is 88 % for the breath test¹⁷. The incidence of PEI is also greatly influenced by the reconstruction technique²⁸. In the present study, pancreaticogastrostomy was performed, which is more frequently associated with PEI than pancreaticojejunostomy.

Czako *et al.*¹⁶ reported on the interaction between the endocrine and exocrine pancreas. Therefore the possible correlation between those two pancreatic functions was also analysed in the present study. Pancreatic head tumours obstruct the main pancreatic duct, which leads to dilatation of the duct and possible atrophy of the pancreatic remnant. This obstruction is relieved by the PD itself. In the present study, a dilated main pancreatic duct was more frequently observed in patients with a postoperative low MTG breath test, which was to be expected. At an endocrine level, new-onset diabetes patients whose endocrine function improved after PD had an enlarged main pancreatic duct at the transection site more frequently than the patients who did not improve.

The strength of our study lies in the fact that patients were evaluated with proper preoperative function tests on endocrine and exocrine level, where others studies are only based on 'history of diabetes' and 'fasting or random glycaemia'. Therefore, the preoperative classification of the patient population is more solid.

One of the weaknesses of our study is the limited time of follow up in some patients. The postoperative control tests had to be performed before starting chemotherapy or before patients were sent back to the referring peripheral centres. On the other hand, follow up of glucose metabolism is an ongoing process after pancreaticoduodenectomy and is often neglected because oncologic patients have other concerns. Accurate long-term follow up data are therefore very scarce.

Some authors²⁹ have also found volumetric assessment as a predictor for new-onset diabetes after distal pancreatectomy. The present study evaluated this for patients undergoing pancreaticoduodenectomy, but there were not enough patient with imaging at the adequate timing to draw conclusions, this finding is still part of an ongoing study.

Quality of life of the impact of pancreaticoduodenectomy on endocrine and exocrine function was not included in this study.

In conclusion, endocrine pancreatic function can improve after PD, especially in patients with newly diagnosed diabetes, and is correlated with preoperative bilirubin levels ($p=0.045$). Progression towards diabetes was, in multivariate analysis, correlated with C-peptidogenic index T_{30} ($p=0.037$). A total of 69.0 % of patients with a preoperative normal MTG breath test experienced postoperative deterioration of the exocrine function. In multivariate analysis, this was correlated with an intervention for a malignant lesion ($p=0.016$).

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Table 5: Univariate and multivariate analysis (only $p < 0.1$ included)

Predictor for deterioration of endocrine function	Univariate analysis			Multivariate analysis		
	OR	95 % CI	p value	OR	95 % CI	p value
Patients operated for premalignant / malignant lesion	9.75	2.01 – 47.38	0.005			
Waist circumference	0.92	0.83 – 1.01	0.081			
Main pancreatic duct dilated at transection site	3.24	0.93 – 11.45	0.068			
Consistency of pancreatic parenchyma	2.92	0.83 – 10.29	0.095			
C-peptidogenic index at T30	29.27	1.09 – 795.37	0.045	31.52	1.21 – 800.52	0.037
Predictor for improvement of endocrine function						
Bilirubin at moment of surgery	1.11	1.00 – 1.23	0.045			
Predictor for deterioration of exocrine function						
Surgery for premalignant lesion	0.186	0.05 – 0.73	0.015	0.239	0.06 – 0.97	0.046
Main pancreatic duct dilated at transection site	0.368	0.13 – 1.03	0.058			

Table 1: Parameters evaluated with a possible correlation to the functional evolution

Parameters	Formula	Reference
Familial history of diabetes	yes /no	22
Patients operated for	pre-malignant / malignant lesion	
Neoadjuvant treatment	yes /no	
Findrisc		
Preoperative Body Mass Index	weight in kg / (height in m) ²	
Change in weight	postoperative weight - preoperative weight	
Waist	cm	
Bilirubin at moment of surgery	mg/dl	
Bilirubin at moment of surgery	elevated / within normal range	
Preoperative stent placement	yes /no	
Main pancreatic duct dilated at transection site	yes /no	4
Consistency of pancreatic parenchyma	hard /soft	
Parenchymal thickness measured at neck	Diameter parenchyma / diameter main pancreatic duct	4
Parenchymal thickness measured at corpus	Diameter parenchyma / diameter main pancreatic duct	
Fasting Plasma Glucose T ₀	Glycémie T ₀	20,21
Preoperative beta-cell function (B%)	Web based HOMA2 calculator	
Preoperative insulin sensitivity (IS%)	Web based HOMA2 calculator	
Preoperative insulin resistance (IR)	Web based HOMA2 calculator	16
Mixed Triglyceride Breath Test	normal / low	
Mixed Triglyceride Breath Test	cumulative dose percentage	30
Insulinogenic index at T ₃₀	$(I_{30}-I_0) / (G_{30}-G_0)$	
C-peptidogenic index at T ₃₀	$(CP_{30}-CP_0) / (G_{30}-G_0)$	26
Corrected Insuline Response	$I_{30} / [G_{30} \times (G_{30}-3.89)]$	
Insulinogenic index at T ₁₂₀	$(I_{120}-I_0) / (G_{120}-G_0)$	30
C-peptidogenic index at T ₁₂₀	$(CP_{120}-CP_0) / (G_{120}-G_0)$	
Matsuda Index	$10000 / (G_0 \times I_0 \times G_{mean} \times I_{mean})^{1/2}$	31
Insulin : glucose ratio T ₀	I_0 / G_0	32
C-peptide : glucose ratio T ₀	CP_0 / G_0	30
C-peptide ratio T ₃₀	CP_{30} / CP_0	33
C-peptide ratio T ₁₂₀	CP_{120} / CP_0	33
Insulin ratio T ₃₀	I_{30} / I_0	33
Insulin ratio T ₁₂₀	I_{120} / I_0	33
Glucagon Δ C-peptide	$CP_6 - CP_0$	4
AUC C-peptide / AUC Glycemia	$\{[(30-0) \times (CP_0 + CP_{30}) / 2] + [(60-30) \times (CP_{30} + CP_{60}) / 2] + [(120-60) \times (CP_{120} + CP_{60}) / 2]\} / \{[(30-0) \times (G_0 + G_{30}) / 2] + [(60-30) \times (G_{30} + G_{60}) / 2] + [(120-60) \times (G_{120} + G_{60}) / 2]\}$	34
AUC Insulin / AUC Glycemia	$\{[(30-0) \times (I_0 + I_{30}) / 2] + [(60-30) \times (I_{30} + I_{60}) / 2] + [(120-60) \times (I_{120} + I_{60}) / 2]\} / \{[(30-0) \times (G_0 + G_{30}) / 2] + [(60-30) \times (G_{30} + G_{60}) / 2] + [(120-60) \times (G_{120} + G_{60}) / 2]\}$	34

Table 2: Patient characteristics (MTG breath test = ^{13}C -labelled mixed-triglyceride breath test)

	Median	Range
Age (Y)	66	38 86
Sex (M/F)	45 / 33	
Preoperative BMI (kg/m ²)	25.1	15.8 35.6
	n = 78	%
Tumour type		
Adenocarcinoma	59	75.6
NET	6	7.7
IPMN or mucinous cyst	4	5.1
Presumed malignancy but no tumour in pathological examination	9	11.5
Preoperative glycaemic status		
History of diabetes	21	26.9
Newly diagnosed diabetes	22	28.2
Prediabetes (IFG, IGT or both)	22	28.2
Normal	13	16.6
Indication for surgery		
Malignant or presumed malignant lesion	67	85.9
Premalignant lesion	11	14.1
Neoadjuvant treatment	4	5.1
Preoperative exocrine insufficiency based on MTG breath test	16	20.5
Preoperative cumulative % of ^{13}C -CO ₂ recovery (median, range)	33.66	5.44 53.87
Preoperative HbA1c in % (median, range)	5.8	4.5 9.1
Finnish Diabetes Risk Score (median, range)	9	2 20
	Median	Range
Days Intensive Care Unit	3	1 26
Hospital stay	21	12 104
Follow up in days	189	28 1541

Table 3: Endocrine function in patients with malignant and non-malignant lesions according to their postoperative pathological diagnosis

	Malignant lesion		Non-malignant lesion		p value
n	60		18		
Male / Female	35	25	10	8	ns
age (median, range)	67	38-86	64	38-78	ns
BMI preoperative (median, range)	25.1	15.8-35.6	24.6	18.1-35.4	ns
BMI postoperative (median, range)	22.9	13.9-32.4	22.2	18.1-34.1	ns
HbA1c preoperative (median, range)	5.8	4.5-7.5	6.3	4.7-9.1	ns
HbA1c postoperative (median, range)	5.5	4.1-7.4	5.6	5.2-7.8	0.059
Preoperative beta-cell function according to HOMA2	110	10-189	110	18-170	ns
Preoperative insulin sensitivity according to HOMA2	54.8	15.7-212.7	76.8	26.3-161.6	ns
Preoperative insulin resistance according to HOMA2	1.82	0.47-6.37	1.3	0.62-3.8	ns
FINDRISC	8	2-20	11	6-20	ns
Preoperative endocrine function					ns
known diabetes	17	28.4%	4	22.2%	
newly diagnosed diabetes	19	31.6%	3	16.6%	
prediabetes	17	28.4%	5	27.7%	
normal OGTT	7	11.6%	6	33.3%	
Evolution endocrine function					
non-progression (n,%)	34	56.7%	8	44.4%	ns
progression (n,%)	7	11.7%	7	38.9%	0.014
improvement (n,%)	19	31.6%	3	16.7%	ns
→ improvement from newly diagnosed diabetes (n,%)	14	23.3%	1	5.5%	0,084

Table 4: Evolution of endocrine function before and after pancreaticoduodenectomy

Entire group	n=78	Preoperative		Postoperative		p value
		Median	Range	Median	Range	
BMI	kg/m ²	25.1	15.8 - 35.6	22.8	13.9 -34.1	< 0.001
Plasma glucose T ₀	mg/dl	101	75 - 349	96	78 -132	ns
Plasma glucose T ₁₂₀	mg/dl	181	51 - 552	155	66 -339	ns
HbA1c		5.6	4.5 - 8.07	5.5	4.7 -6.3	ns
Fasting serum insulin	pmol/L	48	10 - 211	32	2 -128	0.008
Fasting serum C-peptide	nmol/L	0.82	0.30 - 2.37	0.47	0.18 - 0.99	< 0.001
C-peptidogenic index T ₃₀		0.25	0.45 - 0.95	0.18	0.20 - 0.76	< 0.001
Glucagon Δ C-peptide	nmol/L	0.56	0.03 - 2.35	0.22	0.01 - 0.90	< 0.001
HOMA2 beta cell function	%	108	10 -188	80.3	89 - 166	< 0.001
HOMA2 insulin sensitivity	%	55.4	15.7 - 212.7	94.6	41.8 - 262.9	< 0.001
HOMA2 insulin resistance		1.81	0.47 - 6.37	1.06	0.38 - 2.39	< 0.001

Subgroup analysis						
C-peptidogenic index T ₃₀						
Non-progressors	n = 42	0.31	0.05 - 0.69	0.21	0.05 - 0.53	ns
Progressors	n = 14	0.30	0.14 - 0.95	0.20	0.04 - 0.75	0.010
Improvers	n = 22	0.19	0.06 - 0.70	0.18	0.02 - 0.42	ns

Figure 1: Evolution of endocrine and exocrine function after pancreaticoduodenectomy

Figure 2: Analysis of the evolution of the endocrine function according to postoperative pathological diagnosis: malignant and non-malignant lesions separately.