Determinants of glucose control in patients with chronic pancreatitis

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Abstract

Aims/hypothesis Diabetes frequently develops in patients with chronic pancreatitis (CP). Partial pancreatectomy has emerged as a treatment option for such patients. We addressed whether the development of diabetes in CP patients is related to pancreatic beta cell area or clinical variables, and which factors predict the diabetes risk after partial pancreatectomy.

Methods Fractional beta cell area was determined in pancreatic tissue samples obtained from 114 CP patients undergoing pancreatic surgery and related to measures of glucose control, as well as clinical and anthropometric data. Seventy-four patients without diabetes at the time of surgery were contacted again 2.5 ± 1.0 years after partial pancreatectomy in order to obtain information about the post-operative development of diabetes.

Results In the surgical samples in the whole cohort, pancreatic beta cell area was $0.40 \pm 0.06\%$ in patients with and $0.64 \pm 0.06\%$ in those without previously known diabetes

($p=0.039$). There was an inverse non-linear relationship between pancreatic beta cell area and fasting glucose concentrations ($r=0.29$) as well as HbA_{1c} levels ($r=0.36$). Nineteen out of 74 previously normoglycaemic patients (26%) developed diabetes over an average period of 2.5 years of follow-up. Pre-operative fasting glucose levels, HbA_{1c} and BMI were identified as predictors of diabetes after partial pancreatectomy. However, pancreatic beta cell area did not differ in those who subsequently developed diabetes ($0.66 \pm 0.15\%$) and those who did not ($0.62 \pm 0.08\%$, $p=0.45$).

Conclusions/interpretation Hyperglycaemia in CP patients is associated with reduced beta cell area. However, reduced beta cell area does not predict the development of diabetes, suggesting that other factors are more important determinants of alterations in glucose metabolism in patients with CP.

Keywords Beta cell area · Chronic pancreatitis · Diabetes · Glucose control · Inflammation · Pancreas · Pancreatic surgery

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Abbreviations

CP Chronic pancreatitis
CT Computed tomography
IFG Impaired fasting glucose
NFG Normal fasting glucose

Introduction

The pathogenesis of diabetes involves a variable combination of reduced beta cell mass, beta cell dysfunction and insulin resistance [1–4]. In type 2 diabetes, hyperglycaemia has been associated with a deficit in beta cell mass of ~20–65% of normal [5–11], and studies in rodent models of

autoimmune diabetes or in patients with newly onset type 1 diabetes indicate that the extent of beta cell loss amounts to ~50–70% around the manifestation of type 1 diabetes [12–14]. Diabetes is also frequently found in patients with chronic pancreatitis (CP), secondary to the inflammatory process within the pancreas [15–17]. Previous studies have shown that beta cell mass is also significantly reduced in patients with CP, even though the islet destruction appears to occur relatively late during the clinical course of the disease [17]. However, conflicting data have been reported with regard to the prevalence of diabetes in patients with CP and its relationship to disease duration [15, 16, 18].

In clinical practice, patients with diabetes secondary to CP are often characterised by the early need for exogenous insulin supplementation [16]. Whether the onset of hyperglycaemia and the quality of glucose control in these patients are directly related to the islet destruction within the pancreas is yet unclear. In addition, the impact of other risk factors, such as age and BMI, on the risk of developing diabetes in patients with CP has been less well studied.

Pancreatic surgery has emerged as a potential treatment option for patients with CP and severe intractable abdominal pain resistant to conservative analgetic treatment [19, 20]. Indeed, the quality of life has been shown to improve significantly after partial pancreatectomy in patients with persistent abdominal pain due to CP [21]. However, as beta cell mass is also reduced substantially by a partial pancreatectomy, any such intervention bears the potential risk of promoting the development of diabetes [22, 23]. Therefore, it is important to identify clinical predictors of postoperative hyperglycaemia in order to allow for a better risk–benefit assessment before subjecting such patients to pancreatic surgery.

On that background, we addressed the following questions: (1) Is there a relationship between pancreatic beta cell area and glucose control in patients with CP? (2) What clinical characteristics are associated with the development of diabetes in patients with CP? (3) What are the predictors of postoperative diabetes development in patients with CP undergoing partial pancreatectomy?

Methods

Study design Pancreatic tissue was obtained from 114 patients undergoing pancreatic surgery for CP between February 2004 and September 2007. Fractional beta cell area was determined in all tissue samples, and various measures of glucose control and results of clinical laboratory tests as well as anthropometric data were collected from the patients' records by retrospective analysis. The study protocol was approved by the ethics committee of the

Ruhr-University Bochum (registration number 2528), and all patients gave informed consent before surgery.

Patients In total, 114 patients (74 men, 40 women) undergoing pancreatic resections in the Department of Surgery, St Josef-Hospital, Ruhr-University Bochum, between February 2004 and September 2007 were included. The clinical diagnosis of CP was confirmed by an independent pathologist in all cases. Proximal pancreaticoduodenectomies were performed in 94 patients, distal pancreatectomies were carried out in 15 patients and the entire pancreas was removed in five patients. Thus, in 98 patients the pancreatic head was examined, whereas in the remaining 16 patients the pancreatic tail was available. Pancreatic surgery was performed because of chronic abdominal pain resistant to analgetic medication, pancreatic duct obstruction or unclear pancreatic imaging results potentially suspicious for carcinoma. The clinical causes of CP included chronic alcohol consumption in 50 patients, structural pancreatic abnormalities (pancreas divisum) in 14 patients, autoimmune pancreatitis in three patients, benign pancreatic adenomas in four cases, obstructions of the common biliary duct or the papilla Vateri in four patients and hereditary pancreatitis in two cases. One patient developed CP after an episode of acute biliary pancreatitis, and in 36 patients the aetiology of CP remained cryptic. One hundred and four patients were treated with pancreatic enzyme preparation, whereas ten patients did not receive any enzyme supplementation.

The presence of diabetes was determined by careful evaluation of the patient history as well as by the use of glucose-lowering medication. Thus, diabetes was previously known in 28 patients (treated with insulin in 15 cases, sulfonylureas/meglitinides in two cases, metformin in two cases, oral combination therapies in two cases and diet in seven cases), whereas the other patients had no history of known diabetes. The mean diabetes duration was 72.9 ± 99.2 months.

Data collection All patient records were evaluated to collect anthropometric data and information about concomitant medical conditions, current drug medication and relevant laboratory results. Furthermore, all fasting glucose values recorded pre-operatively during the hospital stay were recorded. An average of 5.2 ± 4.9 fasting glucose values was recorded to calculate the mean fasting glucose concentrations. The diagnosis of diabetes was based on the patients' histories as well as on the pre-operative use of glucose-lowering agents.

Prospective follow-up All patients undergoing pancreatic surgery were contacted again in October 2008 after a mean follow-up time of 2.5 ± 1.0 years (range, 1.2 and 4.2 years) after pancreatic surgery. By these means, information about

the vital status, the postoperative manifestation of diabetes, the date of the initial diagnosis of CP and the duration of symptoms suggestive of CP were obtained.

Pancreatic tissue processing Pancreas was fixed in formaldehyde and embedded in paraffin for subsequent analysis as previously described [24]. Sequential 5 μ m sections were stained for insulin using a guinea pig anti-insulin antibody (#A 0564; DAKO, Glostrup, Denmark; lot no. 00001500) at 1:400 dilution and an alkaline phosphatase/RED detection system (DAKO Real Envision Detection System, #K 5007 and #K 5005; lot no. 00025382 and lot no. 00025812, respectively).

Morphometric analysis For the determination of the fractional beta cell areas, the entire pancreatic sections stained for insulin were imaged using a Zeiss Axioplan microscope equipped with a motorised stage $\times 100$ magnification ($\times 10$ objective). A tile image of the tissue section was generated using the 'Mosaix' tool of the software Axiovision, version 4.5. The fractional areas of the pancreas stained positive for insulin were digitally quantified using a colour-based threshold using Zeiss Axiovision software as previously described [24]. One pancreatic tissue section per case was included in this analysis. In order to minimise the potential error induced by the heterogeneous distribution of the islets within the pancreas, the entire pancreatic tissue section available was included in this analyses. By these means, a mean ($\pm$ SD) tissue area of 1.24 ± 1.05 cm² (range 0.21–6.84 cm²) per patient was analysed.

In order to determine the intra- and inter-observer error of these determinations, 20 pancreatic sections were analysed twice by the same investigator as well as independently by two different investigators. These analyses yielded an intra-observer variability of 6.0%, and an inter-observer variability of 8.5%.

Calculations and statistical analysis Patient characteristics are reported as means $\pm$ SD; results are presented as means $\pm$ SEM. All variables were compared by two-sided *t* tests. A *p* value < 0.05 was taken to indicate significant differences. Correlation analyses were carried out using GraphPad Prism 4 in linear or non-linear regression functions.

Results

Pre-operative determinants of glucose control Diabetes was previously known in 28 patients, whereas 86 patients were free of diabetes before surgery by history. When fasting glucose concentrations were used as an additional diagnostic tool, 57 patients presented with normal fasting

glucose (NFG); impaired fasting glucose (IFG) was found in 24 patients, and 33 patients were classified as having diabetes. Pancreatic beta cell area was $0.40 \pm 0.06\%$ in patients with previously known diabetes and $0.64 \pm 0.06\%$ in those patients in whom diabetes had not been diagnosed before hospital admission ($p = 0.039$)—and $0.72 \pm 0.08\%$ in NFG patients, $0.48 \pm 0.06\%$ in IFG patients and $0.39 \pm 0.05\%$ in diabetic patients, when the fasting glucose concentrations were also considered ($p = 0.0084$; Fig. 1).

There was a non-linear inverse relationship between fasting glucose levels and pancreatic beta cell area ($r = 0.29$; Fig. 2). In a similar fashion, pre-operative HbA_{1c} levels were inversely related to beta cell area ($r = 0.36$, $p = 0.020$; Fig. 2). These relationships were no longer detectable when the relationships between beta cell area and either fasting glucose or HbA_{1c} levels were examined individually in the groups of patients with and without diabetes. There was no significant association between BMI and either fasting glucose or HbA_{1c} levels (details not shown).

In order to identify which factors were associated with the presence of diabetes in CP patients, various variables were compared between the patients with and without previously known diabetes (Table 1). These analyses revealed significant differences only for age ($p = 0.0033$) and pancreatic beta cell area ($p = 0.038$). By contrast, body weight, BMI and the duration of CP were not associated with the diagnosis of diabetes in these patients.

Predictors of postoperative glucose control After the follow-up period of 2.5 ± 1.0 years, nine out of the 114 patients undergoing pancreatic surgery had died (8%), six patients (5%) were lost to follow-up, five patients (4%) were excluded because total pancreatectomies had been performed, and in 20 of the remaining patients (18%) diabetes had already been present before pancreatic surgery. Among the 74 patients eligible for the follow-up study, 19 (26%) had developed diabetes during the postoperative

Fig. 1 Fractional beta cell area of the pancreas in 114 patients with chronic pancreatitis. Patients were grouped according to previous diagnosis of diabetes mellitus (a) or fasting glucose concentrations determined during the hospital stay (b). The *p* values were 0.039 for (a) and 0.0084 for (b). Data are presented as means $\pm$ SEM; statistics were carried out using the Student's *t* test (a) or ANOVA (b), respectively

Fig. 2 Relationship between fasting glucose concentrations (**a**) or HbA_{1c} levels (**b**) and the fractional beta cell area of the pancreas in patients with chronic pancreatitis. Dashed lines indicate the regression lines calculated by non-linear regression analyses using a hyperbolic function. The calculated *r* values were 0.29 and 0.36 for (**a**) and (**b**), respectively

follow-up period. In order to identify which factors determined the development of diabetes after partial pancreatectomy, all eligible patients without diabetes before surgery were divided into those developing diabetes during

the postoperative follow-up period and those remaining free of diabetes. Based on these analyses, the pre-operative fasting glucose and HbA_{1c} levels, as well as the pre-operative BMI, were identified as predictors of diabetes after surgery (Table 2). However, there was no difference in fractional beta cell area between the patients who did or did not develop diabetes after the partial pancreatectomy (Fig. 3). At the time of partial pancreatectomy beta cell area was $0.66 \pm 0.15\%$ in those who subsequently developed diabetes, whereas in those who did not do so it was $0.62 \pm 0.08\%$ ($p=0.45$). There also was no significant effect of the respective surgical procedure (pancreatic head vs tail resection) on the postoperative risk of diabetes (Table 2).

Discussion

The present studies were designed to examine the association between pancreatic beta cell area and various clinical characteristics and the development of diabetes in patients with CP, and to identify potential predictors of postoperative diabetes development in patients undergoing partial pancreatectomies for the treatment of CP. Based on the analysis of histological and clinical data from 114 patients with histologically confirmed CP, we report that: (1) pancreatic beta cell area is significantly lower in CP patients with diabetes compared with non-diabetic patients; (2) there is an inverse non-linear relationship between pancreatic beta cell area and fasting glucose or HbA_{1c} levels; and (3) obesity and pre-operative fasting glycaemia determine the individual risk of diabetes development after partial pancreatectomy.

Table 1 Characteristics of 114 patients with CP with and without known diabetes before pancreatic surgery

Variable	With diabetes	Without diabetes	<i>p</i> value ^a
Age (years)	57.2±2.1 (28)	48.8±1.4 (86)	0.0033
Sex (% male/female)	79/21 (28)	60/40 (86)	0.11
Body weight (kg)	68.9±2.0 (28)	68.6±1.54 (84)	0.88
Body height (m)	1.75±0.01 (28)	1.74±0.01 (84)	0.76
BMI (kg/m ²)	22.7±0.7 (28)	22.6±0.4 (84)	0.89
Duration of symptoms (months)	71.8±12.6 (25)	69.8±9.1 (73)	0.50
Time since diagnosis (months)	69.5±18 (24)	50.1±7.8 (73)	0.28
Fasting glucose (mmol/l)	7.41±0.34 (28)	5.49±0.09 (85)	<0.0001
HbA _{1c} (%)	7.48±0.24 (26)	5.88±0.08 (52)	<0.0001
Amylase (U/l)	92.5±38.9 (28)	196.0±61.3 (85)	0.35
Lipase (U/l)	34.7±9.9 (18)	73.8±22.0 (57)	0.31
Carcinoembryonic antigen (U/l)	4.2±1.5 (26)	2.9±0.2 (76)	0.24
Carbohydrate antigen 19-9 (U/l)	41.7±18.2 (28)	24.5±4.4 (76)	0.10
Aspartate aminotransferase (U/l)	34.4±5.6 (28)	37.6±8.5 (86)	0.82
Gamma-glutamyltransferase (U/l)	134.5±35.2 (28)	133.1±30.4 (86)	0.99
Alcohol abuse (% current/never/past)	29/39/32 (28)	23/49/27 (79)	0.62
Nicotine abuse (% yes/no/past)	68/25/4 (28)	66/29/5 (80)	0.91

Data are presented as means ± SEM

Numbers in parentheses indicate the total number of patients in whom the respective information was available

^a Fisher's exact test or Student's *t* test

Table 2 Characteristics of 74 patients with CP who did or did not develop diabetes after partial pancreatectomy

Variable	With diabetes	Without diabetes	<i>p</i> value ^a
Age (years)	53.8±2.3 (19)	47.3±1.8 (55)	0.0534
Sex (% male/female)	53/47 (19)	65/35 (55)	0.18
Body weight (kg)	71.4±3.3 (18)	67.0±14.1 (55)	0.25
Body height (m)	1.72±0.02 (18)	1.74±0.01 (55)	0.31
BMI (kg/m ²)	24.1±0.9 (18)	21.9±0.5 (55)	0.030
Duration of symptoms (months)	64.6±19.7 (18)	63.6±8.0 (51)	0.96
Time since diagnosis (months)	43.7±15.5 (18)	45.2±7.8 (51)	0.93
Fasting glucose (mmol/l)	6.11±0.26 (19)	5.24±0.09 (54)	0.0002
HbA _{1c} (%)	6.22±0.18 (14)	5.75±0.08 (31)	0.0096
Amylase (U/l)	48.4±14.1 (18)	90.9±34.3 (55)	0.49
Lipase (U/l)	56.2±14.9 (12)	260.1±91.3 (38)	0.22
Carcinoembryonic antigen (U/l)	3.8±0.8 (16)	2.7±0.2 (49)	0.082
Carbohydrate antigen 19-9 (U/l)	20.7±6.1 (16)	20.7±5.4 (49)	0.998
Aspartate aminotransferase (U/l)	30.2±6.1 (19)	28.5±3.5 (55)	0.81
Gamma-glutamyltransferase (U/l)	63.4±14.7 (19)	168.9±47.6 (55)	0.20
Alcohol abuse (% current/never/past)	18/47/35 (17)	20/49/29 (51)	0.92
Nicotine abuse (% yes/no/past)	59/35/6 (17)	71/23/6 (52)	0.60
Pancreatic resection (% head/tail)	79/21 (19)	85/15 (55)	0.49

Data are presented as means ± SEM

Numbers in parentheses indicate the total number of patients in whom the respective information was available

^a Fisher's exact test or Student's *t* test

An inverse relationship between pancreatic beta cell area and fasting glucose concentrations has previously been reported in patients with type 2 diabetes and non-diabetic patients based on the analysis of autopsy tissue [9]. The present study extends these findings by demonstrating a similar relationship in patients with diabetes secondary to CP and by providing an association between beta cell area and HbA_{1c} levels for the first time.

Nevertheless, the characteristics of type 2 diabetes and diabetes secondary to CP seem to differ substantially from each other: thus, the individual risk for type 2 diabetes is clearly increased in obese individuals [25], most likely as a result of impaired insulin action. By contrast, BMI was not associated with either fasting glucose or HbA_{1c} levels in the present group of patients with CP. Also, the mean BMI of these patients (~23 kg/m²) was far lower than typically found in patients with type 2 diabetes [26]. However, there was a significant difference in BMI between patients developing diabetes after a partial pancreatectomy and those remaining normoglycaemic, even though the mean BMI was still within normal limits in both groups. This suggests that even small differences in body weight can increase the individual risk of diabetes after a partial pancreatectomy. Therefore, it is important to emphasise that the presently reported findings apply to patients with diabetes secondary to CP only and should not be generalised to the group of patients with type 2 diabetes.

The significant association between pancreatic beta cell area and HbA_{1c} levels also suggests that the extent of beta cells in the pancreas is one important determinant of glycaemic control in diabetic patients. This is consistent

with previous studies in patients with type 1 diabetes showing a clear relationship between beta cell function and HbA_{1c} levels during glucose-lowering treatment [27, 28]. The mechanisms underlying this association have not been completely clarified yet, but may involve the effects of endogenous insulin on alpha cell function [29–31] as well as the direct intra-portal drainage of endogenous insulin vs systemic delivery of exogenously administered insulin [32]. Taken together, these studies emphasise the importance of endogenous insulin secretion for glucose control and support the concept of enhancing beta cell function in the treatment of patients with diabetes [33]. However, because the associations between beta cell area and glycaemic control described herein were purely correlative in nature, they do not allow for firm conclusions regarding the causality of this relationship. Thus, it is also possible, that the presence of diabetes had a detrimental impact on beta

Fig. 3 Fractional beta cell area of the pancreas in 74 patients with chronic pancreatitis who did (*n*=19) or did not (*n*=55) develop diabetes within 2.5±1.0 years after partial pancreatectomy. Data are presented as means ± SEM. The *p* value (Student's *t* test) was 0.45

cell area, possibly mediated through the mechanism of glucose toxicity. Consistent with such reasoning, the inverse relationship between beta cell area and glycaemic control was no longer detectable when the groups of patients with and without diabetes were studied separately.

The present results are in support of our previous study about functional predictors of beta cell area in humans [34]. In that study, an even closer association between glycaemia and beta cell area has been found. It is therefore important to bear in mind the differences between these studies. Thus, in the previous experiments oral glucose tolerance tests were carried out under controlled conditions and after prior withdrawal of all glucose-lowering drugs in a group of 33 patients with different pancreatic diseases. By contrast, the present data were based on the fasting glucose levels determined under normal conditions and without prior drug-washout in a large group exclusively comprised of patients with CP. This was done for practicability reasons and in order not to extend the pre-operative time of hospitalisation in these patients. Because of the frequent use of glucose-lowering medication in the patients with diabetes studied herein, it is likely that glucose concentrations of these patients would have been even higher after a drug-washout period. This might explain why the associations between beta cell area and glycaemic control found in this study were weaker than those described in the previous study [34].

Although this study has demonstrated significant differences in beta cell area between patients with and without diabetes, these differences could account for only a small percentage of the overall variations in glycaemia, and there was still a large degree of inter-individual variability in beta cell area within patients exhibiting similar fasting glucose concentrations. This is in agreement with previous studies in the pancreas of patients with and without type 2 diabetes [9, 11], and may on the one hand reflect the limitations associated with the analysis of a single piece of pancreatic tissue, the variability of the morphometric methods applied and the typical fluctuations of fasting glycaemia. On the other hand, the inter-individual heterogeneity in beta cell area could also suggest that glucose control in patients with CP is not only determined by pancreatic beta cell area, but also involves other factors, such as impairments in beta cell function and insulin resistance. Consistent with this, previous studies have demonstrated an impairment of the insulin secretory responses to various stimuli in CP patients, the extent of which seems to clearly exceed the beta cell deficit found in such patients [18, 35].

Some limitations may apply with respect to this study. In fact, even though formally the determination of beta cell mass requires both pancreatic weight and beta cell area [36], only beta cell area was measured in this study. This was done by necessity, because pancreatic weight cannot be

determined in living humans. We have tried to overcome this problem previously by generating a measure of pancreatic volume based on abdominal computed tomography (CT) scans in a controlled subset of patients with CP without any other detectable pancreatic abnormalities [17]. In the present study, the clinical evaluation of the abdominal CT scans had revealed a pancreatic oedema in a considerable group of patients, thereby likely inducing bias with respect to the determination of pancreatic volume. Therefore, the present analyses have been based on the quantification of pancreatic beta cell area only. However, as the variations in pancreatic volume have previously been shown to be relatively small in adult humans [37], the overall impact of this factor would be expected to be rather minor. Furthermore, beta cell area can vary extensively within the pancreas, and this factor might be of particular relevance in patients with CP, in whom different parts of the organ might be unequally affected by the inflammatory process. In this regard, some studies have also reported a preferential abundance of beta cells in the pancreatic tail [11], but this has not been confirmed by others [7, 34]. Nevertheless, the error implied by these factors might have contributed to the great variance in beta cell area observed in this study. In this regard, it should also be noted that more than 90% of the patients studied herein exhibited severe exocrine insufficiency requiring exogenous enzyme supplementation. Because exocrine insufficiency leading to maldigestion has also been shown to have an important impact on glucose control [38], this factor might have added to the variability in glycaemia in these patients.

The results of this study have important clinical implications for the assessment of the individual diabetes risk in patients with CP before a partial pancreatectomy. Thus, even though the overall percentage of patients developing diabetes after the intervention was relatively low (26%), higher pre-operative BMI and fasting glucose levels were significantly associated with the postoperative manifestation of diabetes. As diabetes is associated with an increased morbidity and mortality and may independently worsen the quality of life, these potential risk factors should be borne in mind when subjecting patients with CP to pancreatic surgery. Nevertheless, these data also demonstrate that a large percentage of patients undergoing pancreatic surgery for CP remain free of diabetes, at least over a follow-up period of ~2.5 years.

In conclusion, the present study has established an inverse relationship between pancreatic beta cell area and glycaemic control in patients with CP. However, the large degree of inter-individual variability in beta cell area also suggests that other variables, such as beta cell function and insulin resistance, are also likely to be important for glucose homeostasis in such patients. Furthermore, mild elevations in glycaemia and BMI have been identified as risk factors

for the development of diabetes after partial pancreatectomy. This suggests that metabolic variables should be included in the individual risk–benefit assessment of pancreatic surgeries in patients with CP.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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