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Brief Reports

Long-term recovery of ß-cell function after partial pancreatectomy in humans

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ABSTRACT

Glucose homeostasis is significantly altered immediately after partial pancreatectomy. The present study examined the long-term consequences of a hemipancreatectomy in 10 patients with chronic pancreatitis and 10 patients with benign pancreatic and extrapancreatic tumors. A 240-minute oral glucose challenge was performed before and shortly after pancreatic surgery, as well as after a follow-up of 3.1 ± 0.5 years. Plasma concentrations of glucose, insulin, and C-peptide were determined; and indices of insulin sensitivity and insulin secretion were calculated. In both groups of patients, fasting and postchallenge glucose concentrations were significantly altered immediately after surgery, but returned to preoperative levels at the time of follow-up ($P < .0001$). Postchallenge insulin and C-peptide concentrations were reduced immediately after surgery ($P < .0001$), but were partly normalized at the time of follow-up ($P < .0001$). These changes were not accompanied by improvements in insulin sensitivity (Matsuda index). However, the oral disposition index revealed a significant recovery of β-cell function at the time of follow-up ($P < .05$). These findings demonstrate a capacity for recovery of glucose control after partial pancreatectomy and suggest that β-cell function can improve significantly over time even in adult humans.

1. Introduction

Glucose homeostasis and insulin secretion are significantly altered after a partial pancreatectomy in humans [1]. We have previously reported an approximately 50% reduction of insulin and C-peptide concentrations shortly (30.0 ± 33.9 days) after a hemipancreatectomy in 14 patients with chronic pancreatitis (CP), 13 patients with benign pancreatic tumors or extrapancreatic masses, and 10 patients with pancreatic adenocarcinoma [2]. The present study was designed to evaluate the long-term consequences of this intervention after a follow-up period of 3.1± 0.5 years (range, 2.2-3.8 years).

2. Methods

2.1. Study design and population

A total of 20 patients (12 male, 8 female; age 57.4 ± 13.0 years) who had undergone a pancreatic resection for CP, benign

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pancreatic tumors, or extrapancreatic masses were included. The latter 2 patient groups were reported as controls because they did not show any general alterations in pancreatic pathology. All patients had been participants in a previous study designed to evaluate the immediate metabolic consequences after a 50% partial pancreatectomy [2] and were contacted again after a follow-up period of 3.1± 0.5 years (range, 2.2-3.8 years). In 5 patients (25%), initially, a pancreatic tail resection was performed, whereas the pancreatic head was removed in the other 15 patients. Three (21%) of the patients with CP were lost to follow-up, and one patient (7%) was excluded because total pancreatectomy had been performed in the meantime. Three patients (23%) with benign pancreatic tumors or extrapancreatic masses were lost to follow-up, and all 10 patients with pancreatic adenocarcinoma had died in the meantime. Six patients with CP (60%) had overt diabetes at the time of follow-up. Four of these patients had developed diabetes after pancreatic surgery. At the time of follow-up, 3 patients (30%) with benign pancreatic and extrapancreatic tumors had developed diabetes. Among the diabetic patients, 7 were treated with insulin, one with metformin plus sitagliptin, and one with diet and exercise.

2.2. *Experimental procedures*

In all patients, a 240-minute oral glucose challenge was performed before surgery, immediately after surgery, and after the follow-up period, and the respective changes in the plasma concentration profiles of glucose, insulin, and C-peptide were determined as described [2]. The experiments were performed in the morning after an overnight fast with subjects in a supine position throughout the experiments. All

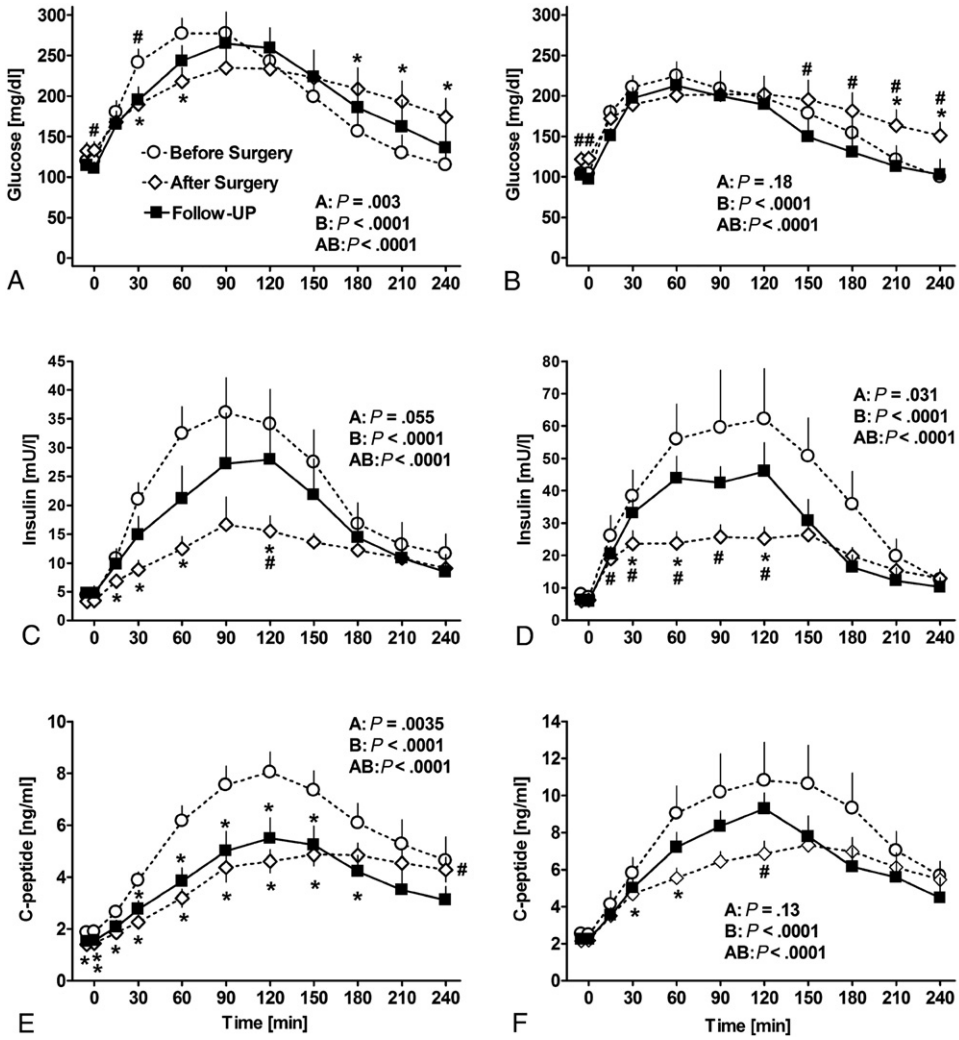

Fig. 1 – Plasma concentrations of glucose (A, B), insulin (C, D), and C-peptide (E, F) in patients with CP (A, C, E; n = 10) and control subjects (B, D, F; n = 10) examined before partial pancreatectomy (open circles), after partial pancreatectomy (open diamonds), and after follow-up (filled square). Statistics were carried out using paired repeated-measures analysis of variance (ANOVA) and denote (A) overall differences between the experiments, (B) differences over the time course, and (AB) differences between the experiments over the time course. *Significant (P < .05) differences at individual time points vs preoperative values (one-way ANOVA). #Significant (P < .05) differences at individual time points vs follow-up (one-way ANOVA).

concomitant medication was withdrawn on the evening of the preceding day. Short-acting insulin was paused on the evening before the tests, and long-acting insulin (neutral protamine Hagedorn in all cases) was allowed until the previous morning.

2.3. Measurements and calculations

The plasma concentration profiles of glucose, insulin, and C-peptide were determined as described [2]. Insulin sensitivity was estimated by the Matsuda index, which takes into account mean insulin and mean glucose levels after oral glucose stimulation [3]. The homeostasis model assessment index of insulin resistance (HOMA-IR) was calculated from fasting glucose and insulin measurements as follows: HOMA-IR = [insulin (microunits per milliliter) × glucose (millimoles per liter)]/22.5. To evaluate pancreatic β-cell function, the HOMA β-cell function index (HOMA-BCF) was calculated as described [4]. Furthermore, to assess β-cell function in relation to the ambient level of insulin sensitivity, the oral disposition index (DI_o) was determined [5]. The DI_o provides a measure of β-cell function adjusted for insulin sensitivity and was calculated as $\Delta I_{0\text{-}30}/\Delta G_{0\text{-}30} \times 1/\text{fasting insulin}$. Insulin-glucose ratios were calculated at all time points before and after oral glucose ingestion.

The study protocol was approved by the ethics committee of the Ruhr-University Bochum. All patients provided written informed consent before study enrolment.

3. Results

3.1. Patients with CP

In patients with CP, fasting glucose levels increased immediately after surgery, but returned to preoperative levels at the time of follow-up ($P < .0001$; Fig. 1, Table 1). The time course of postchallenge glucose concentrations was shifted to a less pronounced increase of glycemia in the early phase (t = 0-120 minutes) and higher glucose levels in the late phase (t = 150-240 minutes) during the immediate postoperative assessment, but this was almost fully normalized at the time of follow-up (Fig. 1). Postchallenge insulin and C-peptide concentrations were significantly reduced immediately after the hemipancreatectomy ($P < .0001$). At the time of follow-up, insulin and C-peptide levels had increased compared with those in the immediate postoperative situation, although by trend they were still lower than levels before surgery. The HOMA index of insulin resistance was higher at the time of follow-up ($P = .03$; Table 1), but the Matsuda index did not reveal any changes in insulin sensitivity over time ($P = .10$). There was no detectable change in HOMA-BCF over the assessment period ($P = .5$; Table 1). However, the 30-minute insulin-glucose ratio was reduced by approximately 45% after surgery; and this was fully reversed at the time of follow-up ($P = .04$). Consistent with this, the DI_o was reduced by approximately 35% after the hemipancreatectomy, but completely normalized over time ($P = .02$).

Table 1 – Metabolic variables determined before and immediately after pancreatic surgery as well as after a follow-up period of 3.1 ± 0.5 years in patients with CP and control subjects (patients with benign pancreatic tumors or extrapancreatic masses)

Parameter (unit)	Before surgery	After surgery	Follow-up	P value [a]
CP				
Glucose tolerance (WHO)				
NGT/IGT/diabetes	0/3/7	1/3/6	0/4/6	.68
Fasting glucose (mg/dL)	118.7 ± 8.1	132.7 ± 10.5 [*,†]	112.4 ± 8.9	.03
HbA_{1c} (%)	6.3 ± 0.6	ND	6.4 ± 0.6	.9
HOMA-IR	1.2 ± 0.3 [†]	0.9 ± 0.1 [†]	1.6 ± 0.4 [*]	.03
Matsuda index	9.2 ± 1.2	11.8 ± 0.7	9.0 ± 1.2	.1
HOMA-BCF (%)	56.1 ± 8.7	61.6 ± 8.9	80.4 ± 24.4	.5
Insulin-glucose ratio, 30 min ($mU \times L^{-1} \times mg^{-1} \times dL$)	0.101 ± 0.055 [†]	0.055 ± 0.01 [†]	0.116 ± 0.001 [*]	.04
DI_o ($[mmol/L]^{-1}$)	0.45 ± 0.1	0.29 ± 0.07 [†]	0.60 ± 0.1	.02
BMI (kg/m^2)	22.5 ± 3.8	ND	24.9 ± 4.0	.28
Control subjects				
Glucose tolerance (WHO)				
NGT/IGT/diabetes	2/5/3	2/3/5	3/4/3	.82
Fasting glucose (mg/dL)	106.9 ± 8.3	112.2 ± 9.1 [†]	99.7 ± 7.3	.02
HbA_{1c} (%)	5.8 ± 1.1	ND	6.1 ± 0.6	.2
HOMA-IR	1.7 ± 0.3	1.7 ± 0.3	1.7 ± 0.2	.9
Matsuda index	6.6 ± 1.1	7.7 ± 1.0	5.9 ±0.7	.4
HOMA-BCF (%)	72.7 ± 15.7	78.0 ± 22.3	81.6 ± 21.6	.9
Insulin-glucose ratio, 30 min ($mU \times L^{-1} \times mg^{-1} \times dL$)	0.243 ± 0.005	0.144 ± 0.03	0.253 ± 0.037	.08
DI_o ($[mmol/L]^{-1}$)	1.2 ± 0.3	0.8 ± 0.2 [†]	1.4 ± 0.3	.03
BMI (kg/m^2)	25.3 ± 4.4	ND	25.7 ± 4.4	.27

Means ± SD. WHO indicates World Health Organization; HbA_{1c}, hemoglobin A_{1c}; NGT, normal glucose tolerance; IGT, impaired glucose tolerance; ND, not determined.

[a] Analysis of variance or χ^2 test.

[*] Significantly different ($P < .05$) vs time point before surgery (Duncan post hoc test).

[†] Significantly different ($P < .05$) vs time of follow-up (Duncan post hoc test).

3.2. *Control patients*

In the control patients, both fasting and postchallenge (*t* = 150-240 min) glucose concentrations were significantly improved at the time of follow-up compared with the early postoperative levels ($P < .0001$; Fig. 1), with no significant differences remaining between preoperative glucose concentrations and the respective levels measured during the follow-up. At the same time, postchallenge insulin and C-peptide concentrations had increased significantly compared with the early postoperative levels ($P < .0001$; Fig. 1), although preoperative levels were still not reached at this time point. Neither the HOMA index nor the Matsuda index suggested any changes in insulin sensitivity over time (Table 1). There were also no significant differences in the HOMA-BCF ($P = .9$). In contrast, the 30-minute insulin-glucose ratio was reduced by trend only directly after surgery ($P = .08$); and the DI_o was reduced by approximately 33% after surgery, which was completely restored at the time of follow-up ($P = .03$). When the patients were grouped according to the respective surgical procedure (pancreatic head resection or pancreatic tail resection), the recovery of insulin secretion at the time of follow-up was observed in a similar fashion in both groups. This finding also remained significant when the patients receiving exogenous insulin treatment were excluded from the analysis (details not shown).

4. Discussion

The present study demonstrates a partial recovery of glucose homoeostasis and β-cell function approximately 3.1 years after a 50% partial pancreatectomy for CP, benign pancreatic adenomas, and extrapancreatic tumors. These results are surprising because we have previously demonstrated the lack of regeneration at the level of β-cell mass after a mean follow-up period of 1.8 ± 1.2 years after partial pancreatectomy in humans [6]. It is therefore most likely that the improvements in glucose and insulin concentrations observed herein were primarily due to a functional recovery of insulin secretion without any changes in β-cell mass. Along these lines, the marked impairment in insulin secretion observed immediately after surgery was likely due to a combination of the actual reduction in the number of β-cells and a functional impairment in insulin secretion, possibly due to the postoperative inflammatory process. Consistent with such reasoning, an inhibition of insulin secretion by inflammatory cytokines has been reported in previous studies [7]. Of note, the improvements in insulin secretion and glucose homeostasis in this study were observed in the absence of any measurable improvements in insulin sensitivity. Aside from the inevitable reduction in β-cell mass, it is possible that other factors, such as alterations in gastrointestinal motility or gastrointestinal hormone secretion, might have contributed to the changes in postchallenge glycemia immediately after surgery. In line with this, the velocity of gastric emptying has been identified as a critical determinant of postprandial glycemia [8]; and changes in gastric emptying are frequently observed after pancreatic surgery [9]. It is therefore possible that a partial recovery of gastric emptying had contributed to the restoration of glucose control over time, although this factor was not directly determined in this study.

It is also important to bear in mind that all patients included in this study underwent surgery for underlying disease conditions, ranging from CP to pancreatic or extrapancreatic adenomas. The impact of a hemipancreatectomy on glucose tolerance in healthy individuals has previously been examined by Kendall and colleagues [1], who found significant impairments in insulin secretion 1 year after surgery. In line with this, Kumar and colleagues [10] recently reported that approximately 43% of previously healthy patients developed abnormal glucose tolerance approximately 5 years after hemipancreatectomy. It is therefore possible that removal of the abnormal tissue (ie, adenomas or areas of local inflammation) has contributed to the long-term improvements in glycemia observed herein.

Taken together, the present findings demonstrate a capacity for recovery of glucose control after partial pancreatectomy and suggest that β-cell function can improve even in the absence of a relevant increase in β-cell mass.

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Conflict of Interest

The authors declare no conflicts of interest.

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