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Hyperalaninaemia is an early feature of diabetes secondary to total pancreatectomy

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Summary. High levels of gluconeogenic precursors have been reported in patients with long-term diabetes secondary to total pancreatectomy. In the present study, blood concentrations of alanine, lactate and pyruvate were measured in six patients undergoing total pancreatectomy and in nine control subjects undergoing major abdominal surgery. To exclude the simple effect of lack of insulin and hyperglycaemia in the development of hyperalaninaemia following total pancreatectomy, three pancreatectomized patients and five control subjects underwent surgical operation while connected to an artificial pancreas. Blood concentration of alanine was constant in the control subjects during surgery (182 ± 20 and 243 ± 31 μmol/l with and without the artificial pancreas, respectively). In pancreatectomized patients basal blood alanine levels were similar to those in control subjects. Blood alanine level rose quickly after removal of the pancreas from 182 ± 24 to 285 ± 15 μmol/l ($p < 0.05$) in the patients connected to the artificial pancreas, and from 198 ± 17 to 395 ± 47 μmol/l ($p < 0.05$) in patients undergoing total pancreatectomy without artificial pancreas. These values were higher than those observed in the control subjects at the end of the operation (192 ± 22 and 230 ± 45 μmol/l with and without artificial pancreas, respectively.) Basal and intraoperative blood concentrations of lactate and pyruvate were similar in pancreatectomized patients and control subjects.

Key words: pancreatogenic diabetes, pancreatectomy, glucagon, alanine, lactate, pyruvate.

Diabetes secondary to total pancreatectomy demonstrates specific metabolic features [1–6]. In particular, high blood concentrations of lactate, pyruvate, and alanine are found in patients who have diabetes after total pancreatectomy [2–6]. Furthermore, in these patients elevated blood levels of several amino acids are found [4, 7, 8]. Alanine and gluconeogenic amino acids are increased, while no significant variation is observed for the branched-chain amino acids [4, 7, 8]. It has been proposed that these metabolic abnormalities may result from a reduced gluconeogenesis rate secondary to chronic glucagon deficiency [3, 4, 6–8]. This is supported by the observation that physiological replacement of the basal glucagon level leads to a significant decline in these metabolites and a fall in gluconeogenic amino acids [8, 9]. However, all these studies were performed in patients after long-standing pancreatectomy and little is known about the time course in the development of these metabolic changes.

The present study was designed to evaluate the relationship between glucagon disappearance from the circulation and the changes in blood alanine, lactate, and pyruvate in patients undergoing total pancreatectomy for pancreatic neoplasia.

Subjects and methods

Subjects

Six patients (four males, two females) undergoing total pancreatectomy for pancreatic adenocarcinoma were studied. The patient's age ranged from 40 to 70 years and body mass index from 20 to 23 kg/m^2. Nine patients with neoplasia (eight males, one female) undergoing major abdominal surgery were studied as controls. These patients were aged 43–73 years and their mean body mass index ranged from 20 to 24 kg/m^2. All subjects gave their informed consent to the study. None had a family history of diabetes. Before surgery, the mean fasting blood glucose concentration was 6.2 ± 0.3 mmol/l in the patients undergoing total pancreatectomy and 5.9 ± 0.5 mmol/l in the control subjects. Each patient received partial parenteral nutrition (glucose 75 g/day) for the 3 days preceding operation. The glucose infusion was stopped 1 h before the beginning of the surgical procedure, and a saline infusion (0.154 mol/l) was maintained thereafter. The same anaesthetic procedure was used in all subjects. Anaesthesia (NLA 2 technique) was induced with thiopental sodium (15 mg/kg) and dehydrobenzoperidol (0.15 mg/kg). Thereafter, it was maintained with fentanyl citrate (25 μg/kg). Mioresolution was obtained with pancuronium bromide (0.25 mg/kg). No patient required blood transfusion during the surgical operation.

To avoid the possible effect of insulin deficiency and hyperglycaemia, three pancreatectomy patients and five control subjects were connected to an artificial endocrine pancreas (Biostator, Life Instruments, Ulm, FGR) 60 min before the beginning of surgery. The remaining patients underwent surgery without insulin infusion.

Methods

In the patients connected to the artificial endocrine pancreas, basal glucose concentrations were maintained throughout the operation by means of an automatic insulin infusion. The rate of insulin infusion was calculated at 1-min intervals by the artificial endocrine pancreas, according to the control algorithm. The operating constants were: for rising glucose levels (KR) = 165, for falling glucose levels (KF) = 45; the inverse of the static gain for insulin infusion (QI) = 30, the basal level at which the basal insulin infusion rate (RI = 15 mU/min) was administered was 4.5 mmol/l (BI). A radial artery was cannulated with a teflon catheter (Angiocath, The Desert Company, Sandy, Utah, USA) for blood pressure monitoring and blood sample collection. After two basal samples, blood (7–8 ml) was drawn from the arterial cannula at 30-min intervals for 360 min from the beginning of the surgical procedure (skin incision). An aliquot (5 ml) of blood was collected in tubes containing 1.2 mg EDTA and aprotinine 500 U/ml (Trasylol, Bayer, Leverkusen, FGR) for the determination of insulin [10], C-peptide [11] and total glucagon immunoreactivity (using 30 K antiserum) [12]. A second aliquot (1.5 ml) of blood was collected in tubes containing 5 ml of 5% percloric acid for deproteinization. After centrifugation at 600 *g* for 15 min, the surnatant was taken up for the fluoroenzymatic assay of glucose, alanine, pyruvate, and lactate [13].

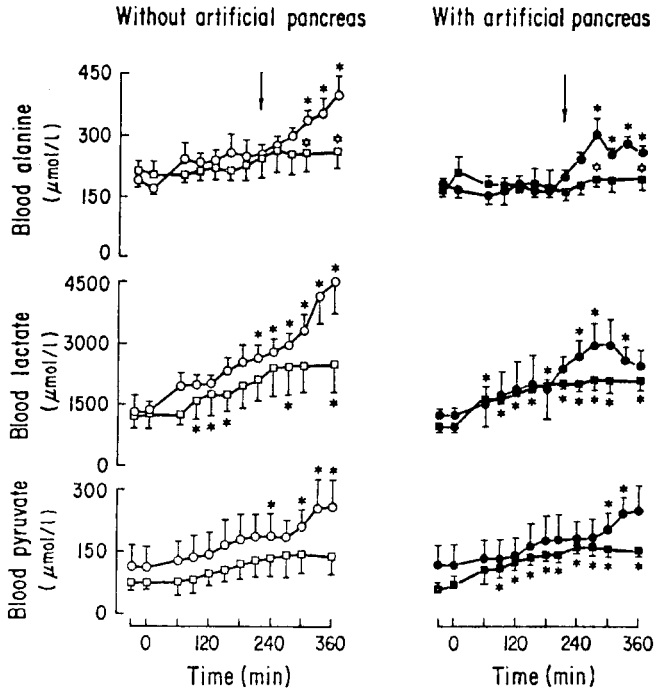

Fig. 1. Blood concentrations of alanine, lactate and pyruvate (mean ± SEM) in patients undergoing total pancreatectomy with (●) or without (○) artificial pancreas, and in control patients undergoing major abdominal surgery (with artificial pancreas = ■; without artificial pancreas = □). Arrow indicates the mean time of functional isolation of the pancreas. *$p < 0.05$ compared with basal values; ☆ $p < 0.05$ between pancreatectomy and control groups

Statistical analysis

All values are expressed as mean ± SEM. Statistical significance was determined by the Studient's t-test and the analysis of variance for repeated measurements [14].

Results

Without artificial pancreas control

The plasma levels of insulin, C-peptide, total glucagon immunoreactivity and blood concentrations of glucose alanine, lactate and pyruvate were comparable in patients undergoing total pancreatectomy and major abdominal surgery (control subjects) at the beginning of the surgical procedure (Table 1, Fig. 1). During surgery blood glucose levels rose progressively in both groups (Table 1). However, at the end of the operation, the blood glucose levels were higher in the pancreatectomy patients than in the control subjects (15.1 ± 0.9 versus, 9.0 ± 0.5 mmol/l, $p < 0.05$). In the pancreatectomy pat-

Table 1. Blood and plasma metabolites and hormone concentrations in patients undergoing total pancreatectomy or major abdominal surgery (control subjects) with and without an artificial pancreas

		Without artificial pancreas		With artificial pancreas	
		Pancreatectomy patients	Control subjects	Pancreatectomy patients	Control subjects
Blood glucose (mmol/l)	Basal	6.8 ± 0.9	5.2 ± 0.4	6.1 ± 0.7	6.9 ± 0.8
	Intra-operative	9.8 ± 1.8	8.9 ± 0.4	5.9 ± 0.7	6.4 ± 0.8
	Final	15.1 ± 0.9[a,b,c]	9.0 ± 0.5	6.1 ± 1.6	6.8 ± 1.4
Plasma insulin (mU/l)	Basal	7 ± 3	5 ± 2	8 ± 3	4 ± 1
	Intra-operative	5 ± 3	5 ± 2	63 ± 10	15 ± 5
	Final	0.5 ± 0.3[a]	6 ± 1	57 ± 7[a]	13 ± 9[a]
Plasma C-peptide (mmol/l)	Basal	0.80 ± 0.27	0.41 ± 0.03	1.32 ± 0.53	0.49 ± 0.15
	Intra-operative	0.08 ± 0.05	0.38 ± 0.07	0.09 ± 0.05	0.32 ± 0.07
	Final	0.06 ± 0.06[a,b]	0.34 ± 0.07	0.07 ± 0.03[a,b]	0.26 ± 0.05
Total glucagon immunoreactivity (pg/ml)	Basal	123 ± 17	122 ± 26	150 ± 35	91 ± 12
	Intra-operative	89 ± 31	156 ± 26	154 ± 33	127 ± 29
	Final	45 ± 9[a,b]	152 ± 39	110 ± 23	129 ± 29

The basal value represents the average of two samples drawn 30 and 15 min before the beginning of surgical procedure. The intraoperative value represents the average of 10–12 samples collected at 30-min intervals during the surgical procedure. The final value represents the samples drawn 360 min after the beginning of the operation. Results are expressed as mean ± SEM.

[a] $p < 0.05$ final versus basal values; [b] $p < 0.05$ between pancreatectomy patients and control subjects; [c] $p < 0.05$ between with and without artificial pancreas groups

ients, plasma concentration of insulin and C-peptide decreased significantly during the surgical operation, so that at the end of the operation the hormone concentrations were significantly lower than in the control subjects (0.5 ± 0.3 versus 6.0 ± 1.0 mmol/l; $p < 0.05$; Table 1). Plasma total glucagon immunoreactivity slightly increased in the control subjects, while it decreased progressively in the pancreatectomy patients (Table 1). In the control subjects, blood alanine concentrations did not change significantly (Fig. 1). In pancreatectomy patients, blood alanine remained constant until the time of the removal of the pancreas. After that, blood alanine increased from 182 ± 24 to 285 ± 15 μmol/l at the end of the operation ($F = 8.915$, $p < 0.01$).

Basal blood concentrations of lactate and pyruvate were similar in both groups. During the operation, however, both blood lactate and pyruvate levels increased progressively (Fig. 1). At the end of operation, blood lactate concentrations were higher, but not significantly different, in the pancreatectomy patients (4450 ± 807 versus 2081 ± 368 μm/l). No differences were found in blood pyruvate concentrations (222 ± 82 and 152 ± 24 μmol/l).

With artificial pancreas control

Basal levels of plasma insulin, C-peptide, total glucagon immunoreactivity and blood concentration of glucose, alanine, lactate and pyruvate were comparable in patients undergoing total pancreatectomy or major abdominal surgery (Table 1). They were also similar to those observed in the patients undergoing surgery without artificial pancreas (Table 1). The basal blood glucose concentration was kept constant throughout surgical procedure and was comparable in pancreatectomy and control groups. The maintainance of constant normoglycaemia required higher concentration of plasma insulin in pancreatectomy patients than in control subjects (57 ± 7 versus 13 ± 9 mU/l; $p < 0.05$). As observed in the patients undergoing surgery without artificial pancreas, the effective removal of the pancreas was documented by the reduction of plasma C-peptide concentration towards the lower limit of detection by the radioimmunoassay (0.07 ± 0.03 mmol/l). Although in the control subjects plasma C-peptide levels declined slightly during surgery, they remained significantly higher than in the pancreatectomy patients at the end of the operation (0.26 ± 0.05 versus 0.07 ± 0.03 mmol/l; $p < 0.05$). Plasma total glucagon immunoreactivity progressively decreased in pancreatectomy patients, while a slight increase was observed in control subjects (Table 1). Blood concentration of alanine, lactate, and pyruvate displayed the same trend observed in the patients undergoing surgery without artificial pancreas (Fig. 1). Blood concentration of alanine remained constant in control subjects throughout the surgical operation. In contrast, in pancreatectomy patients alanine promptly began to rise after the removal of the pancreas (from 198 ± 17 to 395 ± 47 μmol/l; $p < 0.05$). Basal blood concentrations of lactate and pyruvate were similar in pancreatectomy patients (1104 ± 129 and 108 ± 21 μmol/l) and control patients (1218 ± 108 and 68 ± 14 μmol/l). During the surgery procedure both blood lactate and pyruvate levels increased progressively (Fig. 1). Blood concentrations of lactate and pyruvate at the end of the operation were not significantly different between control and pancreatectomy patients (2081 ± 241 versus 2494 ± 482 μmol/l and 144 ± 17 versus 167 ± 18 μmol/l, respectively). There was no significant difference between the pancreatectomy patients receiving insulin and those not connected to the artificial pancreas. When data were analyzed by analysis of variance for repeated measurements, a significant time effect on blood alanine concentration was observed ($F = 21.668$; $p < 0.001$).

Discussion

This study confirms previous observations that hyperalaninaemia is a constant finding in diabetes secondary to total pancreatectomy, and clearly demonstrates that the rise in blood alanine concentration develops rapidly after removal of the pancreas. Hyperalaninaemia has been observed in pancreatectomized animals [15, 16] and man [2–9] and glucagon deficiency has been suggested as a cause for this metabolic abnormality [2–9]. However, in dogs, pancreatectomy does not lead to glucagon deficiency because of a compensatory increase in the secretion of extrapancreatic glucagon. This extrapancreatic glucagon is biologically undistinguishable from the pancreatic glucagon [17–19]. Man after total pancreatectomy is the only known mammal with glucagon deficiency [1–9, 20]. Nonetheless, in individuals after pancreatectomy, other factors such as nutrition, malabsorption, changes in dietary behaviour, abnormalities in gastrointestinal hormone secretion, local recurrence and/or metastatic malignancy, could affect intermediary metabolism and alter blood amino acid profiles. These factors are unlikely explanations in the present study, since the increase in blood alanine concentration was immediately after the removal of the pancreas, suggesting a direct relationship with a pancreatic hormone. Other factors intrinsic to the surgical procedure, such as hyperglycaemia, cannot account for the rise in blood alanine levels. Firstly, the alanine concentration remained unchanged in the control subjects, while in pancreatectomy patients it rose only after the removal of the pancreas. Secondly, the same time-related increase in alanine concentration was observed when blood glucose was kept constant with an artificial pancreas. In patients undergoing total pancreatectomy, the blood alanine level increased both in the presence and absence of circulating insulin concentrations. This finding is in agreement with our previous observations that intensive insulin therapy does not reduce blood al-

anine levels in patients with diabetes secondary to pancreatectomy [6]. We interpret our results as indicating a direct relationship between the disappearance of glucagon from the circulation following total pancreatectomy and the concomitant rise in blood alanine level. Even though total glucagon immunoreactivity did not become undetectable after pancreatectomy, total pancreatic glucagon deficiency can be assumed by the end of the surgical operation. In fact, the completeness of pancreatectomy was confirmed by the decline in plasma C-peptide concentration. To assess further the completeness of pancreatic glucagon deficiency, we chromatographed plasma samples obtained from the portal vein of one subject before and 15 min after an arginine challenge. Following pancreatectomy we detected neglectable amounts of pancreatic glucagon (data not shown). Therefore, the measurable glucagon immunoreactivity in these patients represents the non-specificity of the 30 K antibody which cross-reacts with extrapancreatic glucagonlike material [20–23]. Since the half life ($t_{1/2}$) of glucagon has been estimated to be less than 10 min [24], we can assume that 30 min after removal of the pancreas all patients were virtually aglucagonaemic. With respect to this, it is noteworthy that blood alanine concentrations began to increase 30–60 min after pancreatectomy, and this rise reached statistical significance at 120–150 min. Unfortunately, any conclusion concerning the mechanism(s) underlying the elevation in plasma alanine concentration following acute glucagon deficiency cannot be drawn without the use of radioisotopic kinetic analysis. However, we believe that the most likely explanation underlying the rise in blood alanine concentration following pancreatectomy is reduced liver uptake and a diminished rate of gluconeogenesis. It is now generally accepted that physiological changes in plasma glucagon levels have no direct effect on muscle alanine release [25]. On the other hand, a primary role of glucagon in the regulation of hepatic gluconeogenesis [26] and alanine uptake [27] has been well documented [28]. Our observation are consistent with data published by Boden et al. [29]. These investigators demonstrated that glucagon deficiency, induced in normal subjects by somatostatin infusion, lead to a 23% decrease in plasma alanine concentration. In contrast, Müller et al. [8] replaced physiological glucagon concentration in six patients with total pancreatectomy and demonstrated normalization of alanine levels and other aminoacids. Using similar doses of glucagon in pancreatectomy patients, we were able to demonstrate a similar effect on blood alanine concentration in association with an increase in the rate of glucose recycling [9]. Our data are also in agreement with those reported by Cherrington et al. in dogs [30]. In these animals, the somatostatin suppression of insulin and glucagon was followed by a marked enhancement in alanine levels, as a consequence of a diminished disappearance rate of the amino acid from plasma. In contrast, alanine conversion to glucose was significantly higher when basal portal glucagon levels were replaced than during combined glucagon and insulin suppression. Previous studies have also demonstrated high concentrations of lactate and pyruvate in patients with complete pancreatectomy [2, 3, 6]. It is likely that the elevated concentrations of these metabolites are also due to diminished gluconeogenesis. However, under the present experimental conditions we did not observe any difference in lactate and pyruvate between pancreatectomy patients and control subjects during surgical operation. In both groups the concentrations of the two metabolites increased continuously from the beginning to the end of surgery. High concentrations of lactate and pyruvate have previously been reported after major operations [31]. This is the result of increased extrahepatic production, probably related to an increase concentration of catecholamines [32] and some inhibition of pyruvate oxidation [33]. Glucagon directly stimulates gluconeogenesis by increasing alanine transport across the hepatocyte membrane; in contrast, there is no evidence that the hepatic uptake of lactate and pyruvate is under direct glucagon control [28]. Thus, both increased peripheral production of lactate and pyruvate due to surgical stress, and the absence of a direct glucagon action on liver uptake of the two metabolites can account for the absence of differences between pancreatectomy patients and control subjects. In conclusion, our results indicate that hyperalaninaemia rapidly develops after glucagon deficiency and point out that this metabolic abnormality is a characteristic feature of diabetes secondary to total pancreatectomy.

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