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Long-term follow-up of glycaemic control and parameters of lipid transport after pancreas transplantation

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Summary. We report the long-term metabolic observations made on 37 patients after simultaneous pancreas and kidney transplantation. Plasma C-peptide levels were above the physiological range in all patients and there was no significant difference between patients undergoing delayed duct occlusion (n=12) or those with drainage of exocrine secretion into the urinary bladder (n=25). HbA_{1c} was equally at the upper end of the normal range in both subsets of patients. Mean fasting cholesterol (237 mg/dl) and triglycerides (122 mg/dl) were normal, and HDL-cholesterol was above normal with an average concentration of 77 mg/dl. Two patients underwent an oral fat tolerance test and showed extremely low postprandial lipaemia and very high lipoprotein lipase activities. We conclude that patients with a functioning pancreas graft persistently demonstrate normoglycaemia, elevated C-peptide, and a very favourable lipid profile both in the fasting and the postprandial state.

Key words: Pancreas transplantation – Glycaemic indices – Plasma C-Peptide – Lipids – Lipoproteins

Introduction

Successful pancreas transplantation is at present the only possibility to achieve long-term normoglycaemia and insulin-independence in patients with Type 1 (insulin-dependent) diabetes mellitus (Robertson et al. 1989). However, the procedure is accompanied by peripheral hyperinsulinaemia because the pancreatic venous blood is drained into the systemic circulation rather than into the portal vein (Robertson et al. 1989).

Peripheral (and portal) hyperinsulinaemia are common features of obesity and Type 2 (non-insulin-dependent) diabetes mellitus and are often associated with hypertriglyceridaemia, low HDL-cholesterol, and hypertension (Reaven 1988). In this study, we investigated the long-term effects of pancreas transplantation on plasma C-peptide and glycaemic indices. In addition, we studied lipid and lipoprotein parameters in those patients with primary peripheral hyperinsulinaemia.

Subjects and methods

Patients. In 37 patients with Type 1 diabetes and end-stage diabetic nephropathy, a simultaneous pancreas/kidney transplantation (SPK) was performed, whereby the exocrine pancreatic tissue was either destroyed by delayed duct occlusion (DDO) using an alcoholic prolamine solution (n=12) or pancreas secretion was drained into the bladder (BD, n=25). Details of the surgical procedure and the protocol of follow-up are given in a foregoing article of this volume (Königsrainer et al.). In three patients of each group, graft failure occurred. These six patients were evaluated together. Table 1 summarizes the means (ranges) of the demographic data of the patients with persistent graft function of both kidney and pancreas.

Table 1. Demographic data of patients with persistent graft function

	DDO	BD
n	9	22
sex (female/male)	7/2	6/16
age (years)	40 (19–56)	36 (27–59)
diabetes duration (years)	21 (13–30)	24 (3–37)
height (cm)	164 (155–175)	170 (160–195)
weight (kg)	59 (50–70)	61 (45–74)

DDO = delayed duct occlusion; BD = bladder drainage

Serum creatinine averaged 1.3 mg/dl (range 0.7–2.3) in DDO patients and 1.4 mg/dl (range 0.8–2.4) in BD patients one year after transplantation. The creatinine levels after two years were 1.5 mg/dl (1.1–2.5) in DDO and 1.2 (1.0–1.5) in BD patients.

At monthly intervals, percentage of HbA_{1c} and a diurnal blood glucose profile were determined. Beginning at 21 months after SPK in DDO patients and at 3 months after SPK in BD patients, cholesterol, triglycerides, and HDL-cholesterol were measured every 4 months; C-peptide was determined every 4 months in all patients at 2 h after the subject's usual breakfast in order to obtain a dynamic index of insulin secretion.

For prophylactic immunosuppression, all patients received a triple-drug regimen including cyclosporine A using a priming dose of 3 mg.day^{-1}.kg^{-1} body weight, with subsequent dosage adjustment to plasma levels between 150 and 200 ng/ml; azathioprine 1.5 mg.day^{-1}.kg^{-1} body weight; and prednisone 10 mg/day.

Analytical procedures. All assays were performed in duplicate on a Cobas Mira Autoanalyzer (Roche, Basle, Switzerland). Cholesterol and triglycerides were determined by an automated enzymatic method, details of which have been described elsewhere (Drexel et al. 1988). For measurement of HDL-cholesterol, a dextrane-sulphate precipitation method (Warnick et al. 1982) was used.

Plasma C-peptide was measured by radioimmunoassay (RIA-mat, C-Peptide II, Byk-Sangtec Diagnostica, Dietzenbach, Germany); the normal range is 0.17–0.99 pmol/ml. HbA_{1c} was determined by a microcolumn method (Quick-Sep, Isolab, Oh., USA; normal range 4.2–5.9%) and blood glucose by an automated hexokinase method.

A standardized oral fat tolerance test was performed in two patients as described in detail previously (Patsch et al. 1983). Lipoprotein lipase and hepatic lipase activities were measured at 25°C in post-heparin plasma using specific antisera (Peterson et al. 1985); mean +/- 1SD in 50 healthy probands was 287+/-71 and 604+/-139 nmol NEFA.ml^{-1}.min^{-1}, respectively.

Statistical analysis. Normal range was defined as the mean plus/minus the 2SD interval.

Results

Plasma C-peptide

Figure 1 illustrates C-peptide levels which were above the normal range in all patients with continuous graft function after DDO or BD. In the six patients with graft failure, C-peptide decreased towards the lower end of the normal range around one year after SPK.

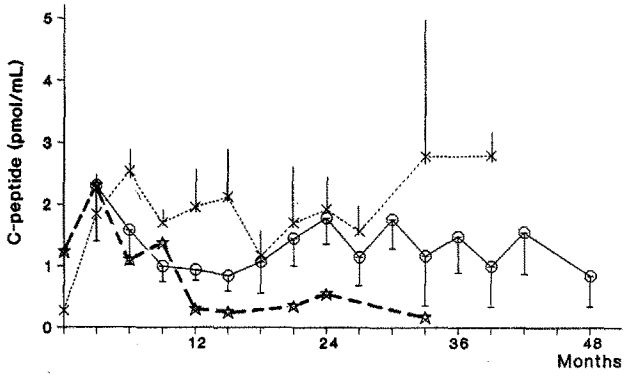

Fig.1. Postprandial plasma C-peptide concentrations. Delayed duct occlusion (DDO): o, solid line; bladder drainage (BD): x, dotted line; DDO and BD patients are described in Table 1; insulin requiring patients:★, broken line

Glycaemic indices

Both mean blood glucose and HbA_{1c} were persistently at the upper end of the normal range. As can be seen from Figure 2, the values for DDO and BD were almost superimposable such that there was no significant difference between the two groups.

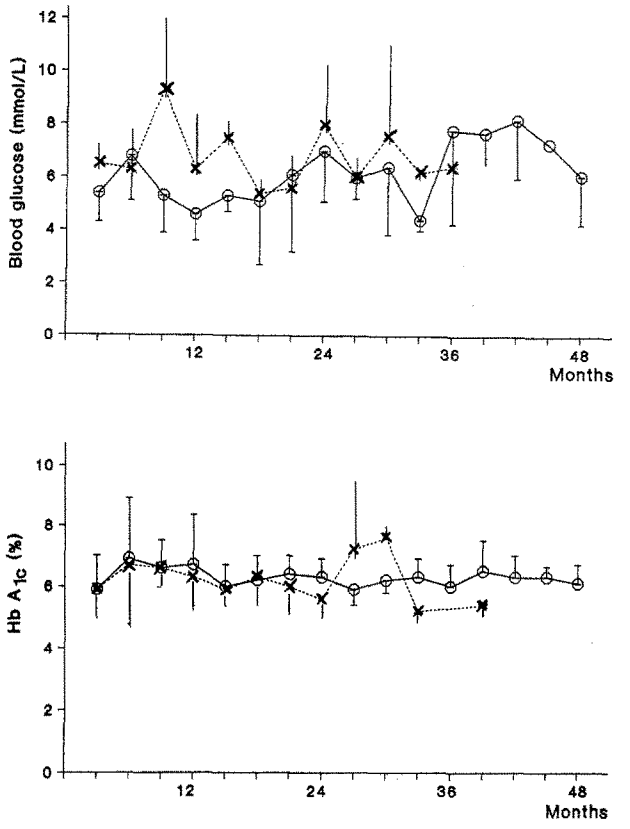

Fig.2. Long-term follow-up of mean blood glucose (upper panel) and HbA_{1c} (lower panel). Delayed duct occlusion: o, solid line; bladder drainage: x, broken line

Fasting lipids

In both groups of patients, triglycerides were always within the normal range with a mean (SD) of 128 (63) and 111 (47) mg/dl, respectively. Cholesterol (Fig. 3) was 230 (32) mg/dl after BD and 241 (33) after DDO; HDL-cholesterol was 87 (14) mg/dl and 68 (15), respectively. In all three parameters, the two groups showed no significant difference and the mean of all measurements from all patients were: cholesterol 237, triglycerides 122, and HDL-cholesterol 77 mg/dl.

Postprandial lipaemia

Two patients underwent the standardized oral fat tolerance test. As shown in Figure 4, the postprandial triglyceride response is extremely low. Postheparin lipoprotein lipase activities were 600 and 711 nmol NEFA.ml^{-1}.min^{-1}, i.e. above the 95th percentile. Hepatic lipase activities were 185 and 312 nmol NEFA. ml^{-1}.min^{-1}, i. e. below the 5th percentile.

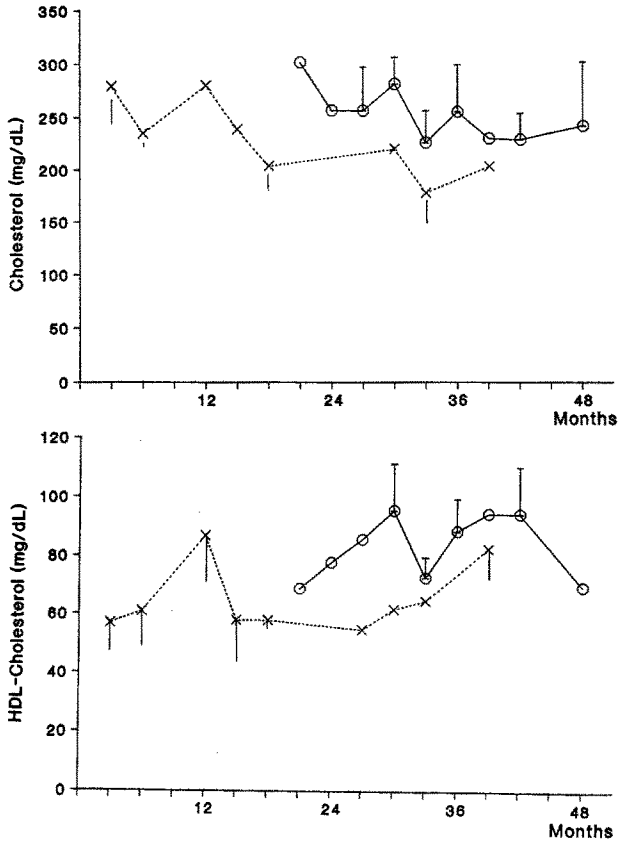

Fig.3. Long-term follow-up of total plasma cholesterol (upper panel) and HDL-cholesterol (lower panel). Delayed duct occlusion: o, solid line; bladder drainage: x, dotted line

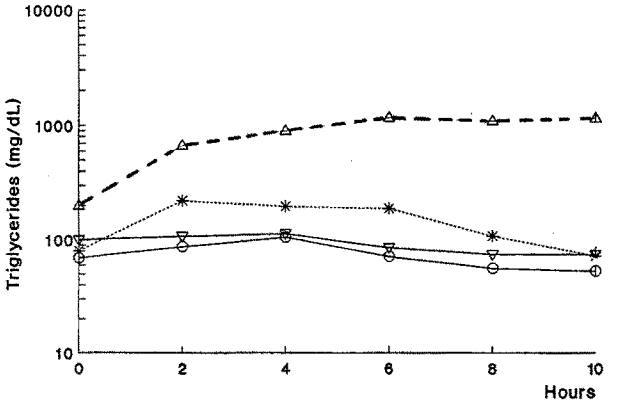

Fig.4. Postprandial triglyceride response in two patients after SPK (v, o, solid lines). For comparison, the response of a normal proband (*, dotted line) and of a patient with Type 2 (non-insulin-dependent) diabetes mellitus (^, broken line) are also depicted

Discussion

This study was designed to determine the long-term effect of different surgical techniques for SPK, i.e. DDO and BD, on C-peptide levels, glycaemic indices, and plasma lipids. In none of the parameters investigated, was there a significant difference between the two techniques suggesting that both afford a very similar functional capacity of the graft. These findings agree with the data of Tyden et al. (1989) who found no differences in fasting blood glucose, glycosylated haemoglobin, and intravenous glucose tolerance for up to 3 years.

With respect to glycaemic parameters, it should be pointed out that, although normoglycaemic, HbA_{1c} was at the upper end of normal. It has been argued that this level of control may not be completely satisfactory, e.g. in pregnancy (Mills et al. 1988), to completely prevent complications.

We found a favourable pattern of lipids and especially of HDL-cholesterol after SPK in both groups. The preliminary data on postprandial fat tolerance are in line with the findings in fasting lipids and indicate a very efficient postprandial triglyceride clearance. Increased activity of lipoprotein lipase, as determined in the two patients, can be explained by peripheral hyperinsulinaemia, because insulin is a potent stimulator of the enzyme. Therefore, primary hyperinsulinaemia as a result of SPK confers a very favourable lipid profile that contrasts sharply with that seen in obese non-diabetic and Type 2 diabetic patients with hyperinsulinaemia, i.e. hypertriglyceridaemia and low HDL-cholesterol. The important difference between the two hyperinsulinaemic states appears to be the fact that, in obesity and Type 2 diabetes, hyperinsulinaemia exists not only in the systemic but also in the portal vascular bed and is probably a result of insulin resistance and, thus, secondary. This suggests to us that hyperinsulinaemia per se does not induce hypertriglyceridaemia in vivo.

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