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# Metabolic risk factors for cardiovascular disease in pancreas and kidney transplant recipients

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**Summary.** Hyperinsulinaemia when combined with insulin resistance and hypertriglyceridaemia is a risk factor for cardiovascular disease. We have studied the serum lipid profile and glycaemic control in 27 uraemic diabetic patients, 23 Type 1 (insulin-dependent) diabetic kidney recipients, 18 non-diabetic kidney recipients, and 30 recipients of kidney and pancreas transplants at 6 months post-transplantation. Fasting serum triglycerides were increased in the uraemic diabetic patients and non-diabetic kidney transplanted patients but not in diabetic kidney transplanted patients whether or not they had received a pancreas. Total cholesterol was increased only in the uraemic diabetic patients while HDL cholesterol was normal in all groups. Whithin the pancreas and kidney transplanted group triglyceride values correlated with glomerular filtration rate ($r = -0.55$) but not with plasma insulin, glycated haemoglobin or $k_G$-value following an intravenous glucose load. Plasma insulin was increased. Whether such isolated hyperinsulinaemia confers an increased risk of cardiovascular disease is not known. There may be adaptive feed-back mechanisms to protect target cells. Increasing the surgical risk in attempts to secure insulin delivery to the portal circulation does not seem warranted.

**Key words:** Pancreas transplantation - Serum lipoproteins - Metabolic control

## Introduction

Population studies have revealed that hyperinsulinaemia is a risk factor for cardiovascular disease (Eschwege et al. 1985; Pyörölä et al. 1985; Welborn and Wearne 1979). As a rule, hyperinsulinaemia is part of a metabolic risk syndrome with insulin resistance, obesity, reduced glucose tolerance and hyperlipidaemia as coexisting risk factors. Resistance to the action of insulin is considered to be the primary disturbance in this context, with hyperinsulinaemia and hypertriglyceridaemia as consequences (Reaven 1988; Ferrari and Weidmann 1990).

Whole organ pancreas transplantation is generally performed with venous drainage to the iliac vein. The first passage through the liver where insulin is normally extracted does not take place and consequently the transplanted patients have high peripheral insulin levels (Luzi et al. 1990). Due to the recognition of hyperinsulinaemia as a risk factor for cardiovascular disease this has been considered a major drawback of the procedure and alternative surgical techniques with venous drainage to the portal veins have been attempted in spite of the considerably increased surgical risk (Calne 1984; Mühlbacher et al 1990).

We have investigated serum lipids and glycaemic control in recipients of pancreas and kidney transplants and compared these with values for uraemic diabetic patients, kidney transplanted diabetic patients and kidney transplanted non-diabetic patients.

## Subjects and methods

*Patients.* 1/: 27 uremic Type 1 (insulin-dependent) diabetic patients who were evaluated for simultaneous pancreas and kidney transplantation. 2/: 23 Type 1 diabetic kidney transplanted patients at routine follow-up during stable conditions. 3/: 18 non-diabetic kidney transplanted patients at routine follow-up. 4/: 30 recipients of pancreas and kidney grafts at follow-up 6 months post transplant. Clinical data are presented in Table 1. The groups were similar with regard to age and body mass index but the proportion of males/females was lower in the non-diabetic kidney transplanted group. All transplanted patients received cyclosporine, except for one diabetic patient who took azathioprine and low dose prednisolone. Prednisolone doses were significantly higher in the recipients of pancreas and kidney grafts than in the two groups of kidney transplanted patients. All patients in the pancreas and kidney transplanted group had been transplanted according to a uniform technique, using the segmental pancreas with exocrine drainage to the urinary bladder and vascular anastomosis to the iliac vessels (Frisk et al. 1987).

*Methods.* Serum lipids were determined in the fasting state. HDL cholesterol was quantitated on fresh serum after precipitation of apo-B-containing lipoproteins (Lopes-Virella et al. 1977). The content of cholesterol in HDL and in total serum (CHOD-PAP, Cat. No. 236691) as well as total serum triglycerides (GPO-PAP, Cat. No 701912) were measured with enzymatic colorimetric tests (Boehringer-Mannheim, Germany) in a Cobas Fara II autoanalyzer (Roche, Stockholm, Sweden).
An intravenous glucose tolerance test was performed in the pancreas and kidney transplanted patients.
Glomerular filtration rate was determined in all three groups of kidney transplanted patients as the plasma clearance of $^{51}$Cr-EDTA following single bolus injection. Insulin was analysed in plasma samples drawn after an overnight fast using a radioimmunoassay kit (Pharmacia Insulin, Pharmacia, Uppsala, Sweden). Glycated hemoglobin, $HbA_{1c}$ was determined by an HPLC-method using ion exchange chromatography on Mono S$^{TM}$ (Pharmacia Fine Chemicals AB, Uppsala, Sweden). The reference interval in young adults is 3.7-5.1 %.

*Statistical analysis.* Unless otherwise stated values are presented as mean±SD. Stepwise multiple regression was calculated with a Macintosh computer using StatView SE software.

**Table 1.** Clinical data and results of metabolic studies (mean ± SD) for the four groups of patients studied

| Patient group | Uraemic diabetic patients | Diabetic kidney transplanted patients | Non -diabetic kidney transplanted patients | Pancreas and kidney transplanted patients |
|---|---|---|---|---|
| Number of patients | 27 | 23 | 18 | 30 |
| Males/females | 19/8 | 14/9 | 11/7 | 21/9 |
| Age, years | | | | |
| median | 37 | 37 | 36 | 37 |
| range | 24-50 | 24-53 | 20-56 | 27-50 |
| GFR ml/min | | 43.4±8.9 | 61.8±15.8 | 50.2±18.2 |
| BMI kg/m$^2$ | 22.0±2.1 | 23.1±2.1 | 24.1±2.7 | 22.7±2.1 |
| Prednisolone dose mg/day | | 8.2±2.5 | 7.4±2.2 | 10.4±1.5 |
| $HbA_{1c}$ % | 8.5±2.1 | 8.7±1.7 | | 5.8±0.7 |
| IVGTT $k_G$-value | | | | 0.80±0.36 |
| Plasma Insulin mU/l | 20±15 | 27±24 | | 24±10 |
| TG mmol/l | 3.0±2.0 | 1.7±0.4 | 2.8±3.1 | 1.7±0.7 |
| Chol mmol/l | 7.1±2.0 | 5.7±1.2 | 6.2±1.5 | 6.0±1.1 |
| HDLmmol/l | 1.3±0.4 | 1.4±0.3 | 1.4±0.3 | 1.3±0.3 |

(BMI= Body mass index, GFR= glomerular filtration rate, TG= serum triglycerides, Chol= total serum cholesterol, HDL= high density lipoprotein cholesterol)

## Results

Results of the metabolic studies are presented in Table 1. Recipients of pancreas and kidney transplants had significantly better metabolic control measured as $HbA_{1c}$ than diabetic patients without a pancreas transplant. However, their mean $HbA_{1c}$ value was above the upper normal limit. The mean $k_G$-value was correspondingly reduced. Fasting plasma insulin was increased to the same extent in pancreas transplanted diabetic patients as in both groups of patients with exogenous insulin treatment.

Serum triglycerides were increased in uraemic diabetic patients and in non-diabetic kidney transplanted control subjects but were normal in diabetic kidney transplanted patients with or without a pancreas transplant. Total cholesterol was increased only in the uraemic diabetic group and HDL cholesterol was normal in all four groups of patients.

In the recipients of combined pancreas and kidney grafts, stepwise multiple regression with serum triglycerides as the dependent variable and GFR, $HbA_{1c}$, plasma insulin and $k_G$-value as independent variables showed a significant correlation only with GFR (n=25, r= - 0.55, F-test 10.54).

## Discussion

The metabolic disturbances found in the pancreas and kidney transplanted patients differ in many respects from those of the metabolic risk syndrome. The patients studied here had hyperinsulinaemia as a result of insulin delivery to the systemic circulation and possibly also due to denervation of the pancreas. The immunosuppressive protocol, which includes corticosteroids, undoubtedly causes some resistance to the action of insulin (Luzi et al. 1990), but this is not a major cause of the hyperinsulinaemia as in the metabolic risk syndrome. In fact, it is not known whether the liver is exposed to increased insulin levels. If not, this might explain why no increase in very low density lipoproteins occurs.

The serum lipid profile is essentially normal in well controlled uncomplicated Type 1 diabetes (Betteridge 1989). The absence of a correlation between the degree

of glycaemic control and serum lipids in our pancreas transplanted patients is, therefore, not surprising. Renal insufficiency, on the other hand, is known to cause hypertriglyceridaemia and hypercholesterolaemia (Attman and Alaupovic 1991). It is obviously a major determinant for serum lipid levels in this clinical situation. The same is true in Type 1 diabetic patients with nephropathy (Attman et al. 1990)

Renal transplant recipients have been reported to have an increased incidence of hyperlipidaemia (Kasiske and Umen 1987; Markell and Friedman 1989). This is in accordance with the finding of hypertriglyceridaemia in our non-diabetic control group. The pancreas transplanted patients, however, had normal serum triglycerides unless their kidney transplant was insufficient. This is difficult to explain because the groups were matched with regard to Body mass index and the higher proportion of males and higher dosage of prednisolone in the pancreas transplanted group would rather bias towards hyperlipidemia. The diabetic kidney transplanted patients also had a normal serum lipid profile. Obviously there may be more subtle disturbances in lipid metabolism in these patients.

Whether hyperinsulinaemia following pancreas transplantation is harmful or not has yet to be decided. It seems reasonable to believe that feed-back mechanisms may protect target cells from the effects of artificially increased levels, by down-regulation of insulin receptors or other adaptive phenomena which have been demonstrated in patients with insulinoma and in experimental studies (Bar et al. 1977; Smith et al. 1976). So far, increasing the surgical risk in attempts to achieve portal drainage does not seem warranted.

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