Metabolic and hormonal control

Metabolic characteristics in patients with long-term pancreas graft with systemic or portal venous drainage

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Summary. Between January 1983 and June 1990, 32 simultaneous pancreas and kidney transplantations were performed at the University of Barcelona. Insulin-secretion was assessed by intravenous glucose tolerance test performed 24h after transplantation and oral glucose tolerance test during the follow-up. Insulin secretion was also studied in seven non-diabetic patients with kidney transplants . Insulin levels in patients with pancreas and kidney transplantations both at the basal level and after glucose stimulation were higher than normal but not different than those observed in patients with kidney transplantation only. Patients with both pancreas and kidney transplantations and kidney transplantation only presented a mild insulin resistance, measured by the glucose/insulin ratio. Insulin levels during the follow-up of a patient with portal venous drainage were similar to those observed in patients with systemic venous drainage. In conclusion, pancreas transplantation allows a long-term maintenance of glucose homeostasis, although coexisting with an insulin resistance, probably related to the immunosuppressive therapy.

Key words: Pancreas - transplantation - insulin - secretion

Introduction

The aim of pancreatic transplantation (PT) is to prevent or ameliorate long-term diabetic complications and to improve the quality of life in patients with diabetes mellitus. It has been demonstrated that PT allows insulin-independence in an increasing number of recipients, although not all of these patients achieve complete normalization of their diabetic metabolism (Landgraf et al. 1990). There is little information about long-term insulin-secretion in patients with PT, but it has been suggested that graft sclerosis after polymer injection, non-portal venous drainage, immunosuppressive treatment (Gunnarsson et al. 1983) and repeated episodes of pancreatitis are factors that can affect Beta cell function over a period of time.

The aim of this study was to evaluate the long-term endocrine graft function in a group of patients with simultaneous pancreas and kidney transplantation (PKTx) and to describe in detail two patients seven years postransplant, one of them with polymer injection and another with portal venous drainage. Insulin-secretion in patients with PKTx was compared with that observed in a group of non-diabetic patients with only kidney transplantation and the same immunosuppressive therapy.

Subjects and methods

Patients. Between January 1983 and June 1990, 32 simultaneous PKTx on Type 1 (insulin-dependent) diabetic patients were performed in our center. We have metabolic information on 22 patients (four women and eighteen men, mean age: 35 ± 1 years and duration diabetes: 19 ± 1 years) in whom insulin-independence was achieved for more than one month.

One patient underwent segmental pancreatic grafting, with the pancreatic duct injected with prolamine. In whole-pancreas transplantated patients exocrine secretion was drained to the ureter in four patients and to the bladder in 17 patients. Direct end-to-end vascular anastomoses between the splenic artery and the vein of the graft and the splenic vessels of recipients were performed in two patients. In the other 20 patients systemic venous drainage was used.

Immunosuppression included azathioprine and prednisone in six patients, cyclosporine and prednisone in one and cyclosporine, azathioprine, prednisone and antilymphocyte globulin in the remaining patients.

Seven healthy volunteers (mean age: 31 ± 1) were studied as a control group. We also performed an oral glucose tolerance test (OGTT) in seven non-diabetic patients with kidney transplant (mean age: 32 ± 1 years) treated with cyclosporine and prednisone (KTx). *Metabolic studies.* 1) Intravenous glucose tolerance test (IVGTT) with 25 g of glucose to measure insulin concentration was performed during the first 24h after transplantation (11 patients). The glucose disposal rate (K value) was expressed as the slope of semilogarithmic decline of blood glucose over time. A K value of more than 1.2% was considered as normal, between 1.2% and 1.0% as borderline and below 1.0% as diabetic.

2) Oral glucose tolerance test (OGTT) with 75 g of glucose to measure insulin and C-peptide, was performed in insulin-independent patients after they were discharged from hospital (16 patients). Abnormal glucose tolerance was determined by the World Health Organization criteria.

The annual follow-up included OGTT and islet cell antibodies (ICA) determination.

Insulin-independence was considered when insulin was no longer required and normal glycosylated haemoglobin and normal daily blood glucose measurements were obtained.

The areas under the curve for insulin and C-peptide during IVGTT and OGTT were calculated as the basal value integrated over the sampling time.

Analysis. Plasma insulin and C-peptide concentrations were measured by radioimmunoassay. ICA were determined by indirect immunofluorescence using human pancreas (group 0) as a substrate (Bonifacio et al. 1987).

Statistical analysis. Results are expresed as mean ± SEM. Student's t-test was used to calculate the significance of differences between mean values.

Results

Although there were no further exogenous insulin requirements, and the patients showed normal daily blood glucose profiles and normal glycosylated haemoglobin, both intravenous and oral glucose tests were abnormal in some patients. IVGTT was normal in six patients (K: $1.48 \pm 0.08\%$), diabetic in four (K: $0.36 \pm 0.09\%$) and non-diagnostic in one (K: 1.05%). OGTT results were normal in 12 patients, diabetic in three and impaired in one.

Basal plasma glucose levels were normal in patients with PKTx but after both IVGTT and OGTT were higher than in the control group (Table 1).

Basal insulin levels in patients with pancreas and kidney transplantation, and throughout IVGTT and OGTT were higher than in the control group (Table 1). Patients with KTx presented basal insulin levels lower than PKTx, however, plasma insulin concentrations in
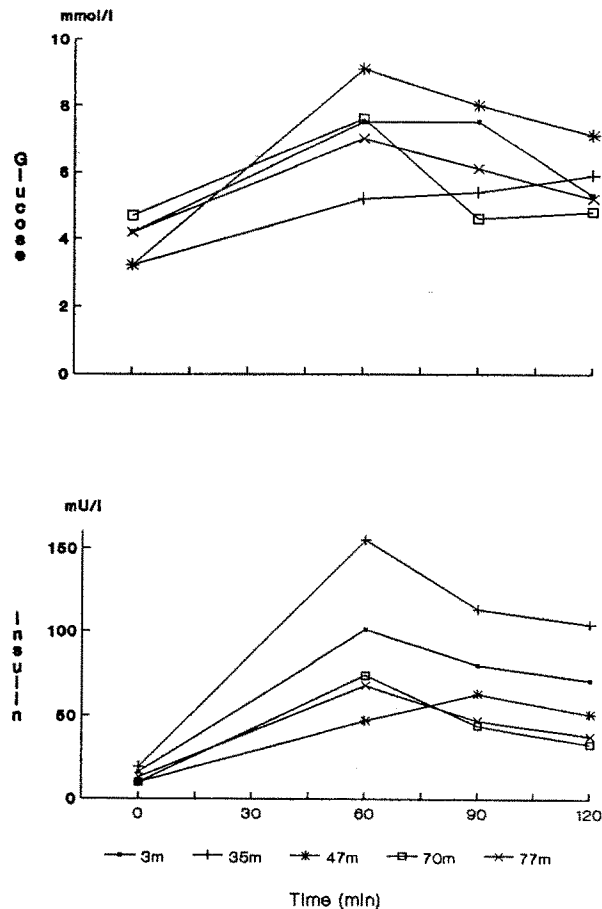

Fig. 1. Oral glucose tolerance test 3, 35, 47, 70 and 77 months after transplantation, in one patient with pancreas and kidney transplantation and pancreatic duct injection with prolamine.
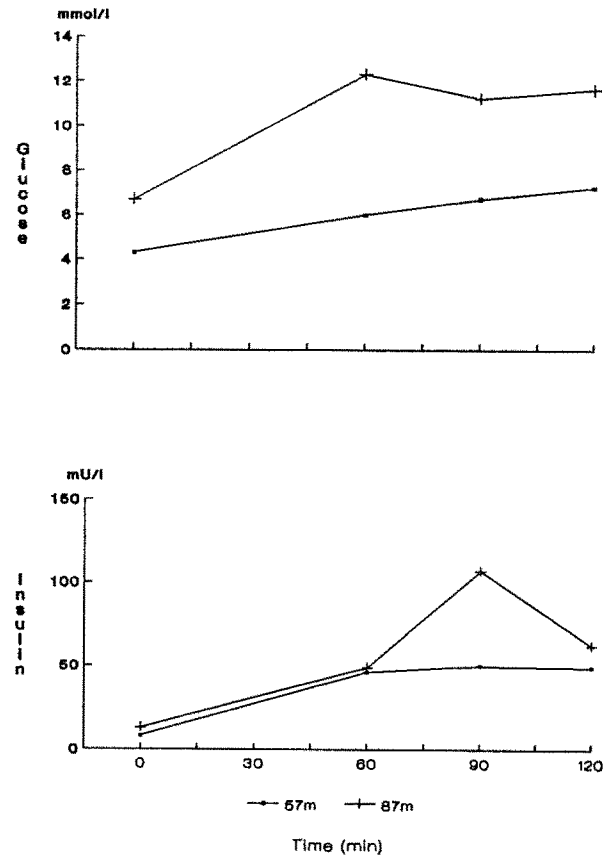

Fig. 2. Oral glucose tolerance test 57 and 87 months after transplantation, in one patient with pancreas and kidney transplantation and portal venous drainage.

Table 1. Blood glucose, serum insulin and C-peptide during intravenous IVGTT and oral (OGTT) glucose tolerance test in patients with kidney and pancreas transplantation (PKTx), in a control group of normal subjects (CG) and in patients with kidney transplantation (KTx).

Time (min)

IVGTT		0	10	20	30	40	50	60
Glucose	PKTx (n:11)	6.3±.9	13.9±.9	12.6±.8	10.8±.7[c]	10±.9	9.7±.9	8.3±.8
(mmol/l)	CG (n:7)	4.8±.2	14.7±.8	10.8±1	7.4±1.3	-	-	4.6±.5
Insulin	PKTx (n:11)	43±8[a]	116±20	108±21	88±17[c]	98±17	83±12	66±7
(mU/l)	CG (n:7)	15±1	82±11	64±8	46±6	-	-	30±9

OGTT		0	60	90	120
Glucose	PKTx (n:16)	4.5±.2	8.3±.5	8.2±.8[c]	8.1±.9[c]
(mmol/l)	CG (n:7)	5±.2	7.1±.7	6±.6	5.6±.7
	KTx (n:7)	4.7±.1	6.6±1.3	6.3±1.1	5.3±.6
Insulin	PKTx (n:16)	37±5[a]	106±13	99±9[c]	98±9[c]
(mU/l)	CG (n:7)	12±1	70±11	62±14	62±14
	KTx (n:7)	15±1[e]	91±11	102±18	95±24
C-Peptide	PKTx (n:16)	2.3±.4[c]	4.3±.6[c]	4.3±.5[b]	4.3±.4[a]
(nmol/l)	CG (n:7)	.4±.1	2.3±.3	2.2±.4	2.1±.4
	KTx (n:7)	1.4±.2[d]	3.7±.4	4.3±.7[d]	4±.9

Results are given as mean ± SEM. [a] p<0.01, [b] p<0.02, [c] p<0.05 pancreas and kidney transplant vs normal subjects. [d] p<0.01 kidney transplant vs normal subjects, [e] p<0.01 kidney transplant vs normal subjects.

both groups of transplanted patients were similar during OGTT (Table 1). C-peptide levels, both basal and postOGTT, in PKTx patients were higher than in the control group but not different than those observed in KTx patients (Table 1). The area under the insulin curve was greater in PKTx in relation to control group (IVGTT: 6318±1119 vs 2951±402 mU.l^{-1}.60 min^{-1}, p<0.01; OGTT: 10664±893 vs 6344± 1108 mU.l.120 min^{-1}, p<0.025) but not different from KTx patients (9096±3437 mU.ml^{-1}.120 min^{-1}). Also, the area under the C-peptide curve was higher in patients with PKTx than in control group (488±61 vs 221±35 nmol.l^{-1}.120 min^{-1}, p<0.025), but similar to the area in KTx patients (406±59 nmol.l^{-1}.120 min^{-1}).

Under basal conditions the glucose/insulin ratio, taken as an indirect parameter to evaluate insulin resistance, was lower in PKTx patients (0.12±0.02) than in control group (0.43±0.1, p<0.001) and in KTx patients (0.31±0.07, p<0.001).

OGTT in one patient with pancreatic duct injection with prolamine, performed 3, 35, 47, 70 and 77 months after transplantation was normal. Insulin and C-peptide secretion during OGTT was also normal (Fig.1). Another patient with portal vein drainage presented an impaired glucose tolerance 87 months after transplantation although she became insulin-inde-

pendent and had a normal glycosylated haemoglobin. Insulin and C-peptide secretion in this case was comparable to patients with systemic drainage (Fig. 2). Both patients had normal kidney function. Immunosuppressive treatment in patient with prolamine duct injection include azathioprine (2.5 mg.kg^{-1}.day^{-1}) plus prednisone (10 mg.day^{-1}) and in patient with portal vein drainage cyclosporine (3 mg.kg^{-1}.day^{-1}) plus prednisone (10 mg.day^{-1}).

ICA determinations were negative throughout the follow-up in PKTx.

Discussion

After successful pancreatic transplantation, glucose levels can be normalized without insulin administration. However, as has been observed by other authors (Landgraf et al. 1990), a certain number of our patients presented with a slightly abnormal glucose tolerance test. However, the usual definition of a normal tolerance test is based on data obtained from non-transplanted patients and may not be entirely accurate in these cases.

Long-term normal insulin secretion can be mantained after successful pancreas transplantation, as we observed

in two patients with 7 years of insulin independency after transplant. The major finding observed in patients with PKTx is the hyperinsulinaemia both at the basal level and after glucose stimulation. Increased plasma insulin levels, with a glucose/insulin ratio lower than in healthy subjects, strongly suggest the existence of peripheral insulin resistance. This condition persists throughout the years, remaining evident in patients at 7 years of follow-up. An interesting point is the insulin resistance aetiology. The existence of similarly high plasma insulin and C-peptide levels after OGTT in PKTx and in non-diabetic patients with kidney transplantation treated with prednisone and cyclosporine, suggests that factors other than pancreas transplantation, probably the immunosuppressive therapy may be involved. It is well known that prednisone impairs glucose metabolism by inducing peripheral insulin resistance (Rizza et al. 1982). Moreover, cyclosporine reduces plasma clearance of prednisone, resulting in an increased prednisone plasma concentration (Ost et al. 1984).

Systemic venous drainage had been blamed for hyperinsulinism. We have studied a patient with a portal venous drainage 57 and 87 months after successful transplantation. On both occasions insulin secretion during OGTT was similar to that observed in patients with systemic venous drainage. This observation does not support the idea that hyperinsulinism in pancreas transplantation is only related to a non-physiological drainage.

It has been suggested that atrophy and fibrosis of the exocrine tissue after duct polymer injection could harm the endocrine tissue. The observation of a patient with a long-term follow-up at 7 years, with a normal Beta-cell function, supports the concept (Secchi et al. 1990) that the duct occlusion method using prolamine as a polymer is a safe technique for management of exocrine secretions.

In conclusion, these data suggest that pancreas transplantation allows for long-term normalization of glucose metabolism, although insulin-resistance is present in all patients. Prednisone treatment, but not systemic venous drainage, could be related to these findings.

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