

Effect of pancreatic and/or renal transplantation on diabetic autonomic neuropathy

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Summary. Thirty-nine Type 1 (insulin-dependent) diabetic patients were studied prospectively after simultaneous pancreas and kidney (n=26) and kidney grafting alone (n=13) by measuring heart rate variation during various manoeuvres and answering a standardized questionnaire every 6 to 12 months post-transplant. While age, duration of diabetes, and serum creatinine (168.1 ± 35.4 vs 132.7 ± 17.7 $\mu\text{mol/l}$) were comparable, haemoglobin A₁ levels were significantly lower (6.6 ± 0.2 vs $8.5 \pm 0.3\%$; $p < 0.01$) and the mean observation time longer (35 ± 2 vs 25 ± 3 months; $p < 0.05$) in the pancreas recipients when compared with kidney transplanted patients. Heart rate variation during deep breathing, lying/standing and Valsalva manoeuvre were very similar in both groups initially and did not improve during follow-up. However, there was a significant reduction in heart rate in the pancreas recipient group. Autonomic symptoms of the gastrointestinal and thermoregulatory system improved more in the pancreas grafted subjects, while hypoglycaemia unawareness deteriorated in the kidney recipients. This study suggests that long-term normoglycaemia by successful pancreatic grafting is able to halt the progression of autonomic dysfunction.

Key words: Autonomic neuropathy – Diabetes mellitus Type 1 – Pancreas transplantation

Introduction

Polyneuropathy affecting the somatic and autonomic nervous system is a common complication of diabetes mellitus. Autonomic neuropathy can affect nearly all organs with a wide spectrum of symptoms and complaints. Once it has developed the patient has a poor prognosis (Ewing and Clarke 1986; Watkins 1990). Various forms of treatment such as continuous subcutaneous insulin infusion (Fedele et al. 1984) or aldose-reductase inhibitors (Jaspan et al. 1983) showed some improvement of autonomic

neuropathy, but these interventions were short. With the increasing success of pancreas transplantation the fate of neuropathy can be studied prospectively for much longer. Studies performed until now focus mainly on cardiorespiratory reflex tests using one or two parameters of standardized reflex tests (Solders et al. 1987; Kennedy et al. 1990) without analyzing autonomic signs and symptoms. Therefore, the effect of functioning pancreatic grafts on autonomic neuropathy was studied prospectively.

Patients and methods

Patients. The study group consisted of 26 Type 1 (insulin-dependent) diabetic patients, 12 men and 14 women (mean age 32 ± 1.6 years, duration of diabetes 23 ± 1 years) who received combined pancreas/kidney-transplantation. Thirteen Type 1 diabetic patients (4 men, 9 women, mean age 33 ± 2 years, duration of diabetes 21 ± 3 years) who underwent simultaneous pancreas- and kidney-transplantation but lost the pancreatic function within three months of transplantation (kidney-alone group) served as controls. For further details see Table 1. The first autonomic test in both groups was performed within eight weeks of transplantation. In the pancreas/kidney group 32 patients were restudied 1 year, 25 after 2 years, and 21 after 3 years. In the kidney-alone group nine patients had a follow-up after 1 year and six patients after 2 and 3 years. Mean observation period was 35 ± 2 months in the pancreas/kidney and 25 ± 3 months in the kidney-alone recipients ($p < 0.05$). All patients were on the same triple drug immunosuppressive therapy consisting of ciclosporin, azathioprine and corticosteroids adapted to the individual requirements. All patients with a functioning pancreas graft required no insulin and had normal HbA₁ values throughout the study. At the last follow-up serum creatinine levels of both groups were comparable (168.1 ± 35.4 vs 137.7 ± 17.7 $\mu\text{mol/l}$), the HbA₁ levels were quite different (6.5 ± 0.1 vs $8.3 \pm 0.3\%$, $p < 0.01$).

Methods. For the assessment of autonomic neuropathy the following standardized methods were used: cardiac autonomic neuropathy was tested by deep breathing (6 breaths/min) with calculation of mean R-R distances, E/I ratio and score (Wheeler and Watkins 1973). Furthermore lying-standing (Dyrberg et al. 1981) and the Valsalva manoeuvre (Levin 1966) were performed and the 30/15 (Dyrberg et al. 1981) and the Valsalva ratio (Levin 1966) were calculated. In addition, a standardized graded questionnaire was used asking for typical signs and symptoms of autonomic neuropathy (Table 2). Changes were evaluated comparing each patient's first and last examination after transplantation.

Statistical analysis. For statistical analysis the Wilcoxon-signed-rank test was used. p-values of less than 0.01 were considered to indicate significant differences. Concerning symptoms evaluated by the graded questionnaire changes of two or more points (in a scale of five possible points) were considered significant. If not stated otherwise values are shown as mean ± SEM.

Table 1. Patient characteristics.

	Pancreas and kidney	kidney-alone
n	26	13
Male/Female	12/14	4/9
Age (years)	32±1.6	33±2
Duration of diabetes (years)	23±1	21±2
Serum creatinine (µmol/l)	168.1±35.4	132.7±17.7
HbA ₁ (normal 6-8%)	6.5±0.1	8.3±0.3 ^a
Immunosuppressive therapy	triple drug	triple drug

values = mean ± SEM, ^a p<0.01

Results

Tachycardia diminished clearly in the pancreas-kidney-group shown by a significant increase of mean R-R-

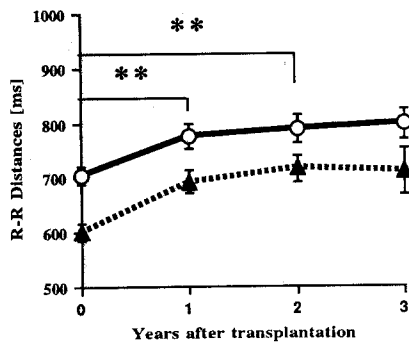


Fig. 1. Mean R-R distances (±SEM) 0, 1, 2, and 3 years after transplantation. The solid line represents pancreas/kidney recipients and the dotted line kidney-alone recipients. **p<0.01

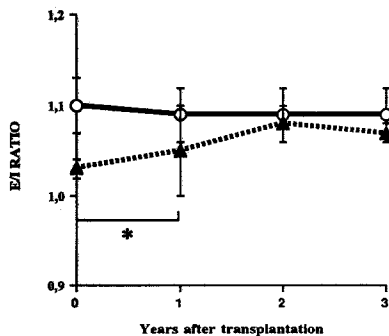


Fig. 2. E/I ratio (±SEM) 0, 1, 2, and 3 years after transplantation. The solid line represents pancreas/kidney recipients and the dotted line kidney-alone recipients. **p<0.05

distances 1 and 2 years after transplantation (p<0.01). R-R-distances slightly increased also in the kidney-alone group, the difference however was not significant (Fig. 1). An improvement of cardiac autonomic neuropathy was seen in the kidney recipients concerning the E/I ratio which showed an increase (p<0.05) 1 year after transplantation (Fig. 2). All other parameters of the various cardiorespiratory reflex tests showed no significant increase or decrease in both groups during the observation period.

Table 2. Clinical symptoms correlated with autonomic neuropathy. The number of patients which improved (+) or deteriorated (-) between the first and last examination after transplantation are shown.

Symptoms	Pancreas and kidney n=26		kidney-alone n=11	
	+	-	+	-
	n	n	n	n
Blood pressure response to standing	1	2	0	2
Orthostatic complaints	2	3	0	0
Symptoms of gastroparesis	0	4	1	0
Diarrhoea	2	1	1	2
Constipation	3	0	0	0
Sweating during night	8	1	0	0
Gustatory sweating	5	2	1	2
Reduced urinary stream	1	2	1	1
Sensation of incomplete bladder emptying	1	3	1	1
Penile erection	1	0	1	1
Retrograde ejaculation	0	0	0	0
Decreased hypoglycaemic symptoms	-	-	0	4
Hypoglycaemic symptoms only at blood glucose levels <2.2 mmol/l	-	-	0	3

Concerning symptoms of autonomic neuropathy related to the cardiocirculatory system there were improvements and deteriorations in both groups without clear differences. Symptoms of gastroparesis worsened clearly in four patients of the pancreas-kidney group and improved in one patient of the kidney-alone recipients. Constipation slightly improved in the pancreas-kidney group, thermoregulatory symptoms clearly improved in the combined transplanted patients and remained unchanged in the kidney-alone group. Reduction of urinary stream or sensation of incomplete bladder emptying occurred more often in the pancreas-kidney group. Penile erection or retrograde ejaculation problems showed no change. About one third of the kidney recipients complained of decreased hypoglycaemic symptoms and/or hypoglycaemic symptoms at blood glucose levels below 2.2 mmol/l within 3 years after transplantation.

Discussion

This study demonstrates that heart rate variation as a parameter of cardiac autonomic function is unchanged 2 to 3 years after successful pancreas and kidney transplantation and in diabetic patients after kidney grafting only. In a former study similar results were reported concerning cardiac autonomic parameters (Solders et al. 1987). However, recently Kennedy et al. (1990) were able to demonstrate a beneficial effect of pancreatic grafting on heart rate variability while cardiac autonomic dysfunction deteriorated in kidney recipients. These obvious discrepancies can be explained at least partially by differences in blood glucose control in the patient groups under study. Our kidney recipients had intensified insulin therapy achieving near normoglycaemia, while the same patient group in the study of Kennedy et al. (1990) showed a much poorer glucose control ($HbA_{1c} > 10\%$). Although under debate (Wheeler and Watkins 1973) Fedele et al. (1984) reported improvements of autonomic neuropathy after intensified insulin therapy. It is therefore important in this kind of study that the study and control groups are comparable with respect not only to the degree of neuropathy but also to kidney function and metabolic control.

Strict glucose control can strengthen severity and prolongation of hypoglycaemia (Dyrberg et al. 1981). When analyzing the questionnaire in this study the most striking finding was that one third of the kidney recipients complained of deteriorating awareness of hypoglycaemia, which can be explained both by the intensified insulin therapy and a progression of autonomic neuropathy. Diaphoresis improved clearly, while symptoms of delayed gastric emptying were higher in the pancreas/kidney group. This can be interpreted also as an improvement of afferent autonomic dysfunction as far as these patients now are able to detect their delayed gastric emptying (Levin 1966). Since symptoms of autonomic neuropathy improved mainly in the pancreas/kidney recipients, it is suggested that long-term normalization of glucose metabolism can halt the progression of autonomic dysfunction. However, the improvements are only marginal within the

observation period of 36 months indicating that severe lesions of the autonomic nervous system present in all our patients are rather "resistant" to amelioration despite long-term normoglycaemia. It is therefore concluded that much longer observation times or patients with earlier stages of diabetic neuropathy are needed to demonstrate marked improvements in diabetic neuropathy. However, even in diabetic subjects with advanced autonomic dysfunction, pancreatic grafting is beneficial since the risk of severe and life-threatening hypoglycaemic attacks due to unawareness of low blood glucose is eliminated.

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