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Time-related, cross-sectional and prospective follow-up of pancreatic endocrine function after pancreas allograft transplantation in Type 1 (insulin-dependent) diabetic patients

R. P. Robertson[1], P. Diem[3] and D. E. R. Sutherland[2]

[1] Diabetes Center and the Division of Endocrinology and Metabolism, Department of Medicine, [2] Department of Surgery, University of Minnesota Medical School, Minneapolis, USA and [3] Diabetes Station, Bern-Inselspital, Bern, Switzerland

Summary. It has been established that successful pancreas transplantation in Type 1 (insulin-dependent) diabetic patients results in normal but exaggerated phasic glucose-induced insulin secretion, normal intravenous glucose disappearance rates, improved glucose recovery from insulin-induced hypoglycaemia, improved glucagon secretion during insulin-induced hypoglycaemia, but no alterations in pancreatic polypeptide responses to hypoglycaemia. However, previous reports have not segregated the data in terms of the length of time following successful transplantation and very little prospective data collected over time in individual patients has been published. This article reports that in general there are no significant differences in the level of improvement when comparing responses as early as three months post-operatively up to as long as two years post-operatively when examining the data cross-sectionally in patients who have successfully maintained their allografts. Moreover, this remarkable constancy in pancreatic islet function is also seen in a smaller group of patients who have been examined prospectively at various intervals post-operatively. It is concluded that successful pancreas transplantation results in remarkable improvements in Alpha and Beta cell but not PP cell function that are maintained for at least one to two years.

Key words: Insulin - C-peptide - Glucagon - Pancreas - Transplantation

Introduction

Transplantation of segments of pancreas from living related donors or whole pancreases from cadaveric donors, when successful, has been demonstrated to be the most effective way to maintain normal glucose homeostasis in Type 1 (insulin-dependent) diabetic patients (Sutherland et al. 1989). However, achievement of this degree of glucoregulation comes with the cost of the operative procedure, patient morbidity and patient mortality. Consequently, before accepting this operation as being effective over time in individual patients, it is essential to examine available data in a time-related, cross-sectional and prospective fashion in recipients with successfully functioning grafts. Using this analytical approach, this manuscript will report the results from intravenous glucose tolerance testing and insulin-induced hypoglycaemia testing to assess secretion of insulin, C-peptide, glucagon, pancreatic polypeptide, as well as intravenous glucose tolerance and glucose recovery from insulin-induced hypoglycaemia.

Subjects and methods

The general patient population as well as the methodology for intravenous glucose tolerance tests (Diem et al. 1990) and insulin-induced hypoglycaemia tests (Diem et al. 1990) have been recently described. Briefly, all recipients were normoglycaemic and had normal haemoglobin A1C levels and none were receiving exogenous insulin or other medication for diabetes. Immunosuppression was achieved with the triple-drug regimen of azathioprine, cyclosporin and prednisone. The duration of diabetes mellitus in the recipients was 22±6 years; the duration after pancreas transplantation was 14±15 months with a range of three to 24 months. Radioimmunoassays for insulin, C-peptide and pancreatic polypeptide were as previously reported (Diem et al. 1990). Calculation for hormonal responses involved subtracting fasting basal levels of the hormone from the three maximal hormone levels following glucose stimulation in the case of insulin and C-peptide. Glucagon and pancreatic polypeptide responses are reported as maximal change over basal encountered during the test period. Glucose recovery is given as the maximal level of recovery expressed as percent of initial glucose level prior to insulin injection. Kg is calculated as the slope of the line reflecting the inverse correlation between time and the natural log rhythm of glucose concentration at 10, 15, 20, 25, and 30 min. after intravenous glucose injection (20 gm).

Results

The acute insulin responses (μU/ml) to intravenous glucose at 3, 12 and 24 months were 119±20, 133±31, and 110±27 for 15, 25, and 14 recipients when the data were analyzed cross-sectionally. None of these values differs significantly from one another (Fig. 1). A similar trend was observed when individual data from 10 patients who had been tested on at least two occasions post-operatively were examined (Fig. 1). Similar trends were observed when C-peptide (nmol/l) responses to intravenous glucose (Fig. 2) were observed. In this case, the values for the acute C-peptide response were 0.97±0.15, 1.14±0.27, and 1.40±5.3 in 14, 19, and 8 patients when data were examined cross-sectionally.

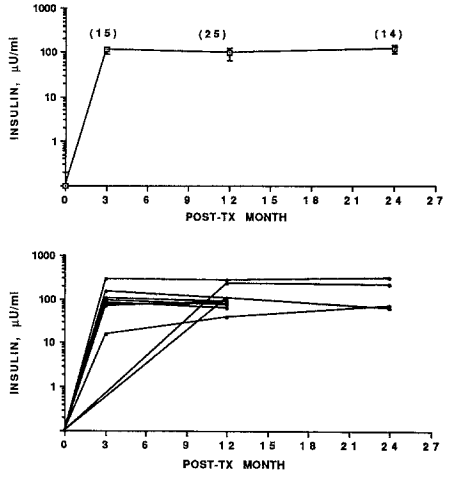

Fig. 1. Acute insulin responses to an intravenous injection of glucose (20g) in recipients of pancreas allografts. Top panel illustrates cross-sectional data over 24 months. Bottom panel illustrates prospective data in ten subjects. TX=transplant.

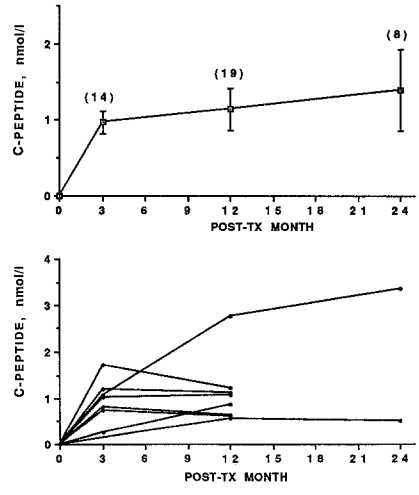

Fig. 2. Acute C-peptide responses to an intravenous injection of glucose (20g) in recipients of pancreas allografts. Top panel illustrates cross-sectional data over 24 months. Bottom panel illustrates prospective data in eight subjects. TX=transplant.

Similar findings were observed in prospectively obtained data from eight patients undergoing testing on at least two separate occasions (Fig. 2).

Fasting plasma glucose levels (mg/dl) at 3, 12, and 24 months post-operatively were 88±11, 86±11, and 80±7 in 15, 24, and 13 recipients (Fig. 3). None of these values were significantly different from one another. Stability in fasting glucose levels was observed when data from ten individual patients who had been studied serially on at least two separate occasions (Fig. 3). Similarly, there was a constancy in the glucose disappearance rates (%/min) at 3, 12, and 24 months with values of 1.49±0.16, 1.53±0.12, and 1.80±3.2 in 14, 24, and 13 recipients (Fig. 3). Glucose disappearance rates also tended to remain stable in ten patients who were examined serially post-operatively (Fig. 3).

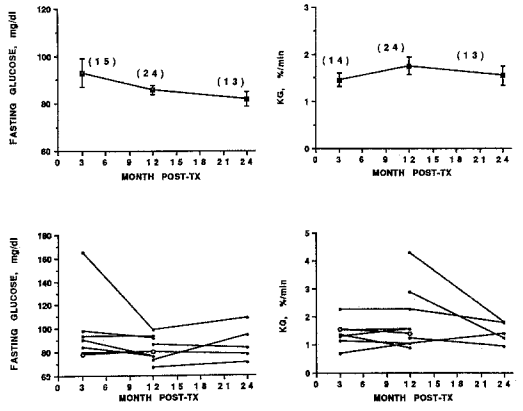

Fig. 3. Fasting glucose levels (left) and glucose disappearance rates (right) after intravenous glucose (20g) injection in recipients of pancreas allografts. Top panel illustrates cross-sectional data. Bottom panel illustrates prospective data in ten subjects.

The ability of recipients to recover from insulin-induced hypoglycaemia was improved as early as three months and they maintained this improvement up to 12 months when data were examined cross-sectionally. The percent recovery in glucose by 60 min. following induction of hypoglycaemia pre-operatively, three months post-operatively and twelve months post-operatively was 40±2%, 64±3%, and 61±2% in 35, 10, and 19 recipients when examined cross-sectionally (Fig. 4). A similar trend was observed when 15 patients were studied prospectively and serially on at least two separate occasions (Fig. 4). This improvement in glucose recovery from insulin-induced hypoglycaemia was associated with an improvement in glucagon secretion during hypoglycaemia. Cross-sectional data obtained pre-operatively, three months post-operatively and twelve months post-operatively revealed maximal glucagon (pg/ml) responses of 39±7, 166±43, and 228±46 in 35, 10, and 18 recipients (Fig. 5).

Improvement in glucagon responses was also observed in 14 patients who had been studied prospectively and serially during the post-operative periods (Fig. 5).

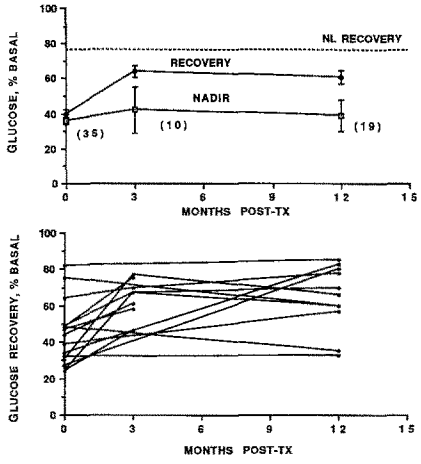

Fig. 4. Glucose nadirs and glucose recoveries after hypoglycaemia induced by intravenous insulin injection in recipients of pancreas allografts. Top panel illustrates cross-sectional data over 12 months. Bottom panel illustrates glucose recovery data studied prospectively in 15 patients.

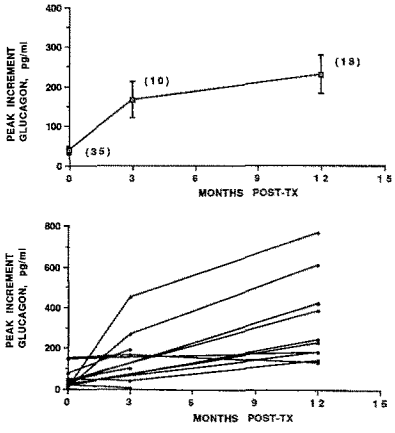

Fig. 5. Peak incremental glucagon responses during insulin-induced hypoglycaemia in recipients of pancreas allografts. Top panel illustrates cross-sectional data. Bottom panel illustrates prospective data from 14 patients.

Discussion

We have previously published that successful pancreas transplantation in Type 1 diabetic recipients restores their ability to respond with biphasic insulin and C-peptide responses during intravenous glucose tolerance testing (Diem et al. 1990). They also attain normal levels of fasting glucose, haemoglobin A1C and intravenous glucose disappearance rates. These results are consistent with earlier more brief reports (Land et al. 1987; Secchi et al. 1987; Ostman et al. 1989) and have been confirmed by a later lengthier report (Osei et al. 1990). We have also previously reported that successful recipients of pancreas transplantation improve their ability to recover from insulin-induced hypoglycaemia and that this is associated with improvements in glucagon responses to hypoglycaemia (Diem et al. 1990). In these reports we found no improvement in pancreatic polypeptide secretion. The only other earlier series reported post-transplant but no pre-transplant data for comparison (Bosi et al. 1988). The current manuscript combines our (Diem et al. 1990) older data with more current data to conduct a time-related, cross-sectional and prospective analysis of endocrine pancreatic function post-operatively in recipients of successfully transplanted pancreas allografts. The results indicate a striking constancy in the improvement of insulin and C-peptide responsivity to intravenous glucose as well as improvement in glucose disappearance rates. Similarly, the improvement in glucose recovery after insulin-induced hypoglycaemia as well as glucagon responsivity to hypoglycaemia is remarkably constant. There is no indication that pancreatic polypeptide responses to insulin-induced hypoglycaemia improve.

It can thus be concluded that pancreas transplantation in Type I diabetic subjects, when successful, results in long-term improvements in pancreatic Alpha and Beta cell function and, consequently, improved glucose homeostasis without the need for exogenous insulin or other agents used to improve glucoregulation in the patients. However, it should be emphasized that there is as yet no concensus as to the medical indications for this procedure. It should be borne in mind that it involves a great deal of expense, patient morbidity and significant patient mortality.

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Dr. R. P. Robertson
The Diabetes Center
Box 101 UMHC
University of Minnesota
Minneapolis, MN 55455
USA