Long-Term Function (6 Years) of Islet Allografts in Type 1 Diabetes

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Eight type 1 diabetic patients, ages 29-41 years, with mean diabetes duration of 23 years (range 18-29 years) received islet transplants from 1 to 5 donors. Seven patients had stable kidney allografts 1-11 years before the islet transplant, and one patient had a simultaneous islet-kidney allograft. Patients' blood glucose control was poor as reflected by the mean ± SD HbA1c of 9.1 ± 1.7% before transplant. Of the first three patients, two (1 and 3) achieved insulin independence for 36 and 38 days, respectively. Two recipients rejected their islet grafts within 1 month (2 and 8) and therefore were excluded from analysis. The HbA1c and insulin requirement of the six remaining patients who had persistent islet function for more than 60 days was significantly reduced from 9.3 ± 1.9 to 6.4 ± 1.0% (P = 0.002) and from 0.75 ± 0.15 to 0.35 ± 0.12 U kg⁻¹ day⁻¹ (P < 0.001), respectively. The two patients with the longest graft survival (4 and 6) achieved a normalization or near-normalization of their HbA1c levels during 6 years in the absence of severe episodes of hypoglycemia. As demonstrated by a decline in C-peptide response during Sustacal challenge tests over a 6-year period, there was a diminution of islet allograft function over time, despite persistence of normal or near normal HbA1c levels. We concluded that transplantation of allogeneic islets with an islet mass comparable with whole or segmental pancreas transplants in type 1 diabetic patients can result in long-term islet allograft function; further, we concluded that, in conjunction with small dosages of exogenous insulin, a functioning islet allograft can result in near-normalization of blood glucose levels and significant improvement in HbA1c. The occurrence of severe hypoglycemic episodes observed for patients in the Diabetes Control and Complications Trial was not observed in recipients with functioning islet transplants, despite the continuous need for exogenous insulin therapy to sustain normal HbA1c over the 6-year follow-up. The significant improvement in metabolic control observed for the patients described in this study, and the potential to significantly decrease or halt the progression of diabetic complications, support the continued application of islet allotransplantation as a treatment modality for type 1 diabetic patients. Diabetes 46:1983-1989, 1997

Over the past 15 years, significant advances have been made in the number and purity of islets that can be harvested from the human pancreas (1-6). Reports of both short-term insulin independence, rendering the first type 1 diabetic patients normoglycemic without the need for insulin therapy in 1990 (7) and long-term insulin independence (8-12), following human islet allotransplantation, encouraged several centers to resume clinical trials of islet cell transplantation in type 1 diabetic patients (13). Although insulin independence has been achieved in some patients, the majority of recipients of an islet allograft still require some exogenous insulin. A detailed analysis reported in the Islet Transplant Registry (13) of 96 pretransplant C-peptide negative type 1 diabetic patients revealed that 27% had a functional graft at 1-year follow-up, but that only 7% of these patients were insulin independent. However, when four characteristics were met—1) mean pancreas preservation time <8 h, 2) transplantation of >6,000 islet equivalents per kilogram recipient body weight, 3) islet transplantation into the liver via the portal vein, and 4) induction of immunosuppression with anti-lymphocyte globuline (ALG)/anti-thymocyte globuline (ATG) and not anti-CD3 monoclonal antibodies (OKT3)-70% of the patients had a functional graft at 1-year follow-up, and 20% were insulin independent (13). Further analysis of 24 islet grafts that fulfilled these four criteria (transplanted 1990-1993) revealed that 10 grafts failed in the early posttransplant period. Exclusion of these early graft losses from the analysis results in a 1-year graft survival rate of ~SO%, a percentage that approaches graft survival observed for solid organs (14).

Studies of the long-term outcome of islet transplantation have rarely been reported (10,15,16), and the potential benefits of islet allotransplantation for type 1 diabetic patients has remained unclear. The aim of the present study was to investigate the benefits of long-term islet allograft function in type 1 diabetic patients.

RESEARCH DESIGN AND METHODS

Patients. Eight patients ages 29-41 years with long-term type 1 diabetes received islet transplants from two (n = 2), three (n = 4), or four or five donors (n = 2) between September 1990 and November 1993. The diabetes duration was 18-29 years, and seven of these patients had stable kidney allografts placed 1-11 years before islet transplant for treatment of end-stage renal disease secondary to type
One patient (5) had a simultaneous islet-kidney transplant. All patients were selected on the basis of their C-peptide negativity, which was verified before their entry into the study by a lack of C-peptide response in a Sustacal challenge test (C-peptide <0.05 pmol/l or <0.3 ng/ml). Informed consent was obtained from each patient, and the study was approved by the Medical Sciences Subcommittee for the Protection of Human Subjects in Research at the University of Miami School of Medicine.

Organ procurement. A negative serum cross-match between donor and recipients and ABO compatibility was required. The cadaveric donor ABO types were the same as the recipient ABO types. The kidneys were obtained from either living related donors (n = 5) or from multiorgan cadaver donors (n = 3). The pancreas grafts were harvested from multiorgan cadaver donors. Venous hypertension of the pancreas during flushing was avoided by venting the portal vein. The pancreateic specimens were immediately immersed in University of Wisconsin (UW) solution and packed in ice.

Islet preparation and administration. Cold ischemia time of the 25 pancreas recipients averaged 7.5 ± 3.4 h (range 5.0-13.5 h). Islets were separated from the pancreas by minor modifications of the automated method for human islet isolation (2,11) using collagenase, type P (1.2-2 mg/ml collagenase solution; Biochrom, Mannheim, Indianapolis, IN). The islets were enriched in a three-layer discontinuous Euroficol gradient (1.108, 1.106, 1.037), in which the digested pancreatic tissue was bottom-loaded with the 1.108 layer. A cell separator (COBE 2991; COBE, Lakewood, CO) was used for centrifugation of the gradients (17). The number, volume, and purity of islets obtained was determined as follows: the final islet preparation was suspended in 250 ml Hanks’ solution, 100 μl samples were then stained with rhodamine (18 mg/ml) to assess total islet yield, and the data were mathematically converted to determine the total number of islets with an average diameter of 150 μm (islet equivalent [IEQ]) (19).

The islet preparation was pelletled and resuspended in supplemented CMRL 1066, followed by overnight culture at 24°C. Before transplantation, the preparation was pelletled and resuspended in 100 ml Hanks’ solution containing 2.5% human albumin; the number of IEQs was determined before transplantation. A mesenteric catheter, placed during laparotomy, was exteriorized, and the patency was maintained for 12-14 days with diluted heparin infusion. The islets were then infused by gravity drainage over a 30 min period on 13 occasions, as determined by the number of islet donors available during OKT3 therapy. In the last two cases, access to the portal vein was achieved by percutaneous transhepatic catheterization of the portal vein (5). Portal venous pressure was measured, and for patients who received more than one islet preparation, the portal vein catheter was flushed every 6 h with 0.2 ml saline containing heparin (100 U/ml). The catheter was removed after completion of the last islet infusion.

Immunosuppression. Patients received OKT3 (5 mg/day i.v.) for 14-16 days, starting 2 days before the first islet cell transplant (patient 5 received OKT3 for only 10 days). Each patient received 500-1,000 mg methylprednisolone daily for the first 3 days of OKT3 therapy. Thereafter, patients 1-4 were given maintenance dosages of methylprednisolone (8-12 mg/day). Patients 5-8 were treated with higher dosages of methylprednisolone, following standard renal transplant protocols. Azathioprine dosage was adjusted according to white blood cell counts. Cyclosporine dosing was adjusted to achieve whole blood trough levels of 250-300 ng/ml.

Posttransplant insulin management and follow-up. For all patients, blood glucose was maintained at 80-140 mg/dl by continuous insulin infusion during the first 14 days posttransplant. Three patients (13) received decreasing dosages of intermediary and regular insulin, subcutaneously, to sustain normoglycemia for 30-60 days. For all other patients, no attempt was made to discontinue insulin administration.

Islet allograft function was evaluated before and at different intervals after transplantation. Variables selected for analysis were 1) basal and peak C-peptide response to 6 kcal/kg Sustacal (40 g carbohydrates, 24 g fat, and 61 g protein) and the calculated Sustacal stimulation index (20); 2) loss of basal C-peptide response, defined as the fit of two consecutive undetectable values (<100 pmol/l) and 3) blood glucose and HbA1c levels.

The two patients with the longest graft survival (4 and 6) were evaluated with the aid of TeleDoc (Better Control Medical Computers, Miami Beach, FL), a new on-line computer system for daily diabetes intervention (21,22); blood glucose and lifestyle (e.g., diet, exercise, stress, hypoglycemia) events were reported 24 hours a day via touch-tone telephone. A voice-interactive interface expert system decoded touch-tone key presses while guiding the patient verbally by a synthetic voiced speech.

Bergman’s minimal model for evaluation of glucose kinetics was used to calculate insulin sensitivity index (23,24).

For patients 4 and 6, euglycemic, hyperinsulinemic (40 μU ml⁻² min⁻¹) clamp studies were conducted as previously described (25,26). In brief, glucose was maintained at 100 mg/dl by available infusion of 26% dextrose. The infusion was adjusted according to glucose determination made every 5 min on a glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). For calculation of insulin sensitivity, we defined the glucose infusion rate as steady state by calculating the average rate over the final hour of insulin infusion (90-150 min). The metabolic clearance rate (MCR) of glucose was calculated by dividing the tissue glucose disposal by the corresponding glucose concentrations (26).

Analysis. Plasma C-peptide and insulin were measured by radioimmunoassay (DPC, Los Angeles, CA), βHb by high-performance liquid chromatography, and plasma glucose levels with a Beckman Glucose Analyzer II (Beckman, Fullerton, CA).

RESULTS

The transplanted islet mass was 478,000-1,271,000 IEQs, or 8,318-21,185 IEQs per kilogram of recipient body weight. In some patients, there was a transient increase in liver function tests after islet transplantation (two- to sevenfold increase in transaminases), which normalized within 34 days after intraportal infusion of the islets. In this series of patients, we did not routinely monitor portal venous pressure, since we had previously demonstrated that there was no significant change in portal venous pressure before and after intraportal infusion of 5-6 ml of tissue (10.8 ± 6.6 and 16.4 ± 7.2 mm HgO, respectively) (5,27). In one of the eight patients (3), we observed an increase in serum creatinine (from 159 to 203 μmol/l) following islet allograft rejection 5 months after islet transplantation. A kidney biopsy obtained at the time of islet allograft rejection was compatible with chronic kidney rejection.

In the other patients, the serum creatinine levels pretransplant and 2 years after islet allograft transplantation did not change significantly (120 ± 7 and 122 ± 12 μmol/l, respectively), and in the two patients with long-term islet function (4 and 6) we did not observe any increase in serum creatinine over a period of 6 years (124 and 124 μmol/l pretransplant, and 115 and 124 μmol/l 6 years posttransplant, respectively). The period of islet allograft function was between 23 and 9253 days. Six patients had a graft function >60 days: 1,125, 3,154, 4, >2353, 3,756, 6, >2,205, and 7,356 days. Patients 1 and 3 were able to discontinue insulin therapy for 36 and 38 days, respectively. For the six patients with >60 days of graft function, prednisolone and prednisolone insulin requirements and HbA1c levels were analyzed. The pretransplant insulin dosage in these six patients was reduced from 45.7 ± 9.3 to 20.9 ± 7.0 U/day or from 0.75 ± 0.15 to 0.35 ± 0.12 U kg⁻¹ day⁻¹ (P < 0.001); the HbA1c decreased from 9.3 ± 1.9 to 6.4 ± 1.0% (P = 0.002) during graft function (Table 1).

Before transplantation, patient 4 was treated with an intensive insulin regimen (see 28, Diabetes Control and Complications Trial [DCCT]) for 6 years. A HbA1c of 7.1% was achieved; six episodes of severe hypoglycemia, each requiring the assistance of another person (spouse, emergency room) were the direct result of intensive insulin therapy. Before islet transplantation, patient 6 had poor diabetes control (HbA1c 9.3%). Although this individual did not experience episodes of severe hypoglycemia, he experienced several (>10) hyperglycemic episodes (requiring urgent outpatient medical intervention) and one episode of ketoacidosis (requiring hospitalization) during the 6 years pretransplant.
TABLE 1
Glucose control and insulin dose

<table>
<thead>
<tr>
<th>Case</th>
<th>Pre-IxTx (U kg(^{-1}) day(^{-1}))</th>
<th>During graft function* (U kg(^{-1}) day(^{-1}))</th>
<th>After graft failure (U kg(^{-1}) day(^{-1}))</th>
<th>Pre-IxTx (%) During graft function* (mean, n ≥ 4)</th>
<th>After graft failure (mean %, n ≥ 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.85</td>
<td>0.27</td>
<td>0.62</td>
<td>7.1</td>
<td>4.8</td>
</tr>
<tr>
<td>2</td>
<td>0.50</td>
<td>NA</td>
<td>0.50</td>
<td>8.5</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>0.81</td>
<td>0.34</td>
<td>0.84</td>
<td>9.8</td>
<td>6.4</td>
</tr>
<tr>
<td>4</td>
<td>0.83</td>
<td>0.34</td>
<td>NA</td>
<td>7.1</td>
<td>5.9</td>
</tr>
<tr>
<td>5</td>
<td>0.52</td>
<td>0.25</td>
<td>0.43</td>
<td>12.0</td>
<td>7.0</td>
</tr>
<tr>
<td>6</td>
<td>0.89</td>
<td>0.31</td>
<td>NA</td>
<td>9.3</td>
<td>6.4</td>
</tr>
<tr>
<td>7</td>
<td>0.63</td>
<td>0.31</td>
<td>0.45</td>
<td>10.4</td>
<td>7.8</td>
</tr>
<tr>
<td>8</td>
<td>0.55</td>
<td>NA</td>
<td>0.55</td>
<td>8.7</td>
<td>NA</td>
</tr>
<tr>
<td>Mean</td>
<td>0.70</td>
<td>0.351</td>
<td>0.57</td>
<td>9.1(\pm)</td>
<td>6.4(\pm)</td>
</tr>
<tr>
<td>SD</td>
<td>0.16</td>
<td>0.12</td>
<td>0.15</td>
<td>1.7</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Calculated, if graft function was > 60 days. HbA\(_{1c}\) normal values: 3.5-6.2%. NA, not applicable. Comparisons between pretransplant and during graft function: \(\hat{p} < 0.001\), \(\hat{p} = 0.002\). IxTx, islet transplantation.

Figures 1A and 1B show the normalization of HbA\(_{1c}\) during the first 2 years after islet transplantation, and maintenance of a normal or near normal HbA\(_{1c}\) level over a 6-year period for recipients 4 and 6, respectively. As shown in Fig. 2A and 2B, the glucose profile (recorded by TeleDoc) for these two patients is very stable, and the average preprandial glucose levels are 4.0-6.7 mmol/l(70-120 mg/dl).

The stimulated C-peptide response to a Sustacal test 1 month posttransplantation in patient 6 showed a near normal response (Fig. 3). Because the half-life of C-peptide is prolonged by about 40% in transplanted patients with only one functioning kidney (29,30), it is difficult to use C-peptide measurements to evaluate and compare insulin secretion. The higher C-peptide levels observed for the transplant patient compared with normal subjects throughout the 5-h study period reflect this longer half-life (Fig. 3).

Figure 4 demonstrates that differences in an immunosuppressive regimen can be associated with profound differences in basal C-peptide levels; the higher dosages of methylprednisolone administered to patient 6 appeared to result in higher levels of basal C-peptide, compared with those observed for patient 4. Two years posttransplant, basal C-peptide levels were comparable with segmental pancreas transplant recipients and normal control subjects (29); however, the observed levels were much lower than those obtained for simultaneous whole pancreas-kidney or kidney transplant alone recipients (29).

Over time, a slight, gradual decrease in insulin secretion appears to occur, as suggested by both the lower C-peptide response observed during the Sustacal test (results not shown) and the lower Sustacal stimulation index (Fig. 5). Figure 6 reveals that insulin levels obtained via frequently sampled intravenous glucose tolerance test (IVGTT) after tolbutamide stimulation decreased significantly over time in patient 6. Because the model for determination of the insulin sensitivity index \(S_1\) requires a substantial insulin secretion after the initial glucose infusion and injection of tolbutamide, the \(S_1\) could not be calculated for patient 4. As assessed by the euglycemic, hyperinsulinemic clamp technique, the MCR of 7.07 ml kg\(^{-1}\) min\(^{-1}\) and M value of 7.0 mg kg\(^{-1}\) min\(^{-1}\) indicate a normal insulin sensitivity 6 years after transplantation in patient 4. For patient 6, the \(S_1\) of 0.58 X 10\(^{-4}\) at 2 months (methylprednisolone 12 mg/day) and 2.43 X 10\(^{-4}\) at 12 months posttransplant (methylprednisolone 6 mg/day) are suggestive of severe insulin resistance. Because endogenous
insulin release is very low after 12 months, we were not able to assess insulin sensitivity with the minimal model. The MCR of 4.29 ml kg\(^{-1}\) min\(^{-1}\) and the M value of 4.98 mg kg\(^{-1}\) min\(^{-1}\), as assessed by the clamp technique, indicated that significant insulin resistance persisted 6 years after islet transplantation in patient 6.

The Sustacal stimulation index (Fig. 5) was lower for the islet allograft recipients than for both normal control subjects and whole pancreas transplant recipients; the decline in the Sustacal index score at 2-3 years posttransplant suggests a reduction in P-cell mass (20).

Normalization of HbA\(_1c\) was achieved in each patient (n = 8) with adjuvant insulin therapy, and none of the patients in our study experienced major hyperglycemic, ketoacidotic episodes, or severe hypoglycemia that required medical treatment. These results represent a striking contrast to those reported by the DCCT (28,52); furthermore, there was no weight gain (weight change: -0.6 ± 2.6 kg) associated with normalization of glycemic control.

**DISCUSSION**

Islet transplantation can result in insulin independence and normoglycemia (11,13,31); however, the islet mass required to constantly achieve these goals has not been clearly defined (5). In the present study, an average of nearly 15,000 IEQs/kg body wt. were transplanted, corresponding to a total IEQ of approximately 900,000 islets. According to state-of-the-art criteria (13), this number is far above the suggested 6,000 IEQ/kg body wt. It has been demonstrated for segmental pancreas transplants that 50% of the distal pancreas can normalize recipient plasma glucose levels (32). If one-half of the estimated 600,000 to 1 million islets per pancreas (33,34) are transplanted, diabetes should be cured, as has been shown for islet autograft recipients (13). The number of islets given to the first three patients, therefore, should have been sufficient to achieve insulin independence. However, one graft was lost after 3 weeks, and two patients achieved insulin independence for 36 and 38 days, respectively, with graft failure at 4 and...
FIG. 3. Sustacal test before (▼) and 1 month after (●) islet transplantation in patient 6 compared with healthy control subjects (○).

5 months posttransplant, respectively. The majority of islet grafts are lost early after transplantation (within the first few weeks) (13). Many of these early graft losses are difficult to explain based solely on the occurrence of classical mechanisms of allogeneic immune recognition and recurrence of autoimmunity. If rejection or/and autoimmunity were the only causes of early graft losses, the discrepancy observed between survival rates of whole pancreas (where early graft losses seldom occur) versus islet allografts early after transplantation should not exist. Moreover, early graft losses still occur in syngeneic islet transplants (35) and in experimental models manipulated to suppress T-cell activation (36–38), suggesting that additional mechanisms might contribute to such phenomena. These include inadequate mass of transplanted β-cells, impaired vascularization, and a nonspecific inflammatory reaction in the host microenvironment at the site of transplantation (39). Unfortunately, little is known about the percentage of islets that experience primary nonfunction or are lost immediately after embolization (33). Because evidence exists that 1) insulin injection can protect islets from destruction in preclinical diabetes, thus postponing or preventing the development of type 1 diabetes (40,41), and 2) hyperglycemia lowers the β-cell mass of islet grafts (42), we elected not to discontinue insulin in subsequent recipients of islet transplants (patients 4–8). Out of these five patients, only one early graft failure occurred (after 1 month), two islet grafts functioned for 1 and 2 years, respectively, and two islet grafts are still functioning at >6 years posttransplantation. We were able to detect significant C-peptide levels (1.22 ± 0.62 nmol/l) 3 months posttransplant (undetectable before transplant) in five of eight patients (63%).

As demonstrated with the frequently sampled IVGTT and Sustacal stimulation test, first- and second-phase insulin secretion and glucose and C-peptide response at 1–2 months after islet transplant are comparable to those observed for normal control subjects. At 2–12 months posttransplant, there is a great reduction in first-phase insulin secretion, suggesting that the number of engrafted islets has been reduced and that the β-cells are functioning at maximal secretory capacity (43). The insulin and C-peptide levels observed for the frequently sampled IVGTT or the Sustacal stimulation test confirm that there is a gradual decline of β-cell function over time. The minimal model, however, does not seem to be the appropriate tool to assess insulin sensitivity in recipients of islet allografts; due to reduced β-cell mass, insulin responses to intravenous glucose and tolbutamide stimulation are too low to calculate the S^' Insulin sensitivity is most likely reduced by immunosuppressive drugs, thus increasing the mass of islets required to maintain normoglycemia.

Because long-term insulin independence (up to 10 years) has been achieved after autologous human islet transplant (44), islet allograft failure in type 1 diabetic patients must be due to chronic rejection, unrecognized acute rejection episodes, or recurrence of autoimmune disease. Recurrent autoimmune disease and β-cell destruction have been observed after whole pancreas (45) and segmental pancreas transplantation in immunocompetent or only minimally immunosuppressed identical twins or HLA-identical siblings (46), as well as in recipients of cadaver pancreatic grafts, despite standard immunosuppressive therapy (47). Insulin treatment may slow the destruction of β-cells considerably, as supported by the findings of Keller et al. (40) in individuals at high risk for type 1 diabetes.

This study demonstrates that, although islet allograft function diminishes over time, even small levels of endogenously secreted insulin, as assessed by C-peptide measurements, can prevent wide glucose fluctuations, thus resulting in normalization of glycemic control and improvement in HbA_1c (48–51). The patients with a functioning islet allograft achieved normal or near normal HbA_1c. The results obtained
are comparable with or superior to those achieved with intensive insulin therapy (28), including results for the two patients who have maintained excellent control for >6 years.

For the two patients with the longest graft survival, the rate of severe hypoglycemia prior to transplant were comparable with the 0.62/patient-year in the intensively treated group (52); however, since islet transplantation, those two patients have had no episode of hypoglycemia requiring treatment. Because it was recently reported that the glucagon response is lost from transplanted intrahepatic islets during hypoglycemia in human recipients of islet allo- and autotransplants (53), and that the defective glucagon response is determined by the transplantation site (54), the absence of severe hypoglycemic episodes in the two patients with the longest graft survival cannot be explained by an intact glucagon response during hypoglycemia. In the DCCT, the strongest predictors of severe hypoglycemic events were a prior history of hypoglycemia and a total deficiency of endogenous insulin production, reflected by a residual C-peptide response of <200 pmol/l, a daily insulin requirement of >0.635 U/kg body wt, and decreased $HbA_1c$ levels (52). Because recipient 6 had a pretransplant $HbA_1c$ of 9.3%, and recipient 4 had a history of severe hypoglycemic episodes, both patients should have been at increased risk for developing hypoglycemia. Based on the DCCT analysis, their incidence of hypoglycemic episodes should have been in the range of 0.70-0.90, compared with 0.19/patient-year in conventionally treated patients with type 1 diabetes (52). By restoring partial endogenous insulin secretion via islet transplantation, normalization of $HbA_1c$ appears to have been achieved by the increased risk of hypoglycemic episodes and weight gain seen in the DCCT.

Because islet transplantation can be performed via percutaneous transhepatic catheterization without significant acute or long-term adverse effects on liver function or portal venous pressure (5,27), it is conceivable that islet transplants could be repeated, as clinically indicated by deterioration of glucose metabolism over time.

We have shown that islet transplantation results in endogenous insulin secretion over a long period of time, and that long-term (6 years) near normalization of glucose metabolism, in conjunction with small dosages of exogenous insulin, can be achieved in patients with islet allografts. Because the complete absence of an insulinogenic reserve is probably the fundamental cause of diabetic brittleness, even a small $\beta$-cell capacity has definite effects on plasma glucose and avoidance of hypoglycemia, as well as on psychological well-being (52,55).

The observation that even continuous immunosuppression cannot prevent a reduction of insulin secretion over time necessitates the development of new strategies to prolong $\beta$-cell graft survival by preventing early graft loss, chronic rejection, or recurrence of autoimmune disease. At present, treatment strategies involving islet transplantation offer the opportunity for good blood glucose control and prevention of diabetic late complications, as shown in the DCCT, but with less hypoglycemia. Normalization of glycemic control has been maintained for >6 years in some cases.

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**References**


