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SHORT REPORT

Over ten-year insulin independence following single allogeneic islet transplant without T-cell depleting antibody induction

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ABSTRACT

Islet cell transplantation is a promising functional cure for type 1 diabetes; however, maintaining long-term islet graft function and insulin independence is difficult to achieve. In this short report we present a patient with situs inversus, who at the time of islet transplantation had a 26-year history of type 1 diabetes, complicated by hypoglycemic unawareness and severe hypoglycemic events. After a single allogeneic islet transplant of a low islet mass, and despite developing de novo anti-insulin and anti-GAD65 autoantibodies, the patient has remarkably maintained insulin independence with tight glycemic control and normal metabolic profiles for 10 years, after receiving prolonged *non*-T-cell depleting immunosuppression.

Introduction

In 2000, Shapiro et al. reported improvement in the efficacy of islet transplantation as a functional cure for type 1 diabetes (T1D) using the Edmonton Protocol, which involved standardizing islet cell isolation procedures, the number (dose) of transplanted islets, and the use of steroid-free immunosuppression.[1] However, only 1 of the 36 recipients from the International Trial of the Edmonton Protocol remained insulin independent after three years.[2] With continuing progress in both islet isolation and clinical management after transplant, the rate of insulin independence following islet transplantation has steadily improved. For patients transplanted between 2007 and 2010, 44% were insulin independent at three years.[3] More recently, our research group demonstrated that 60% of patients remained insulin independent at five years, without the use of T-cell depleting antibody induction immunosuppression.[4] Despite these improvements, in a substantial number of cases, islet cell transplantation is still followed by a gradual decrease in the production of insulin and

partial (to complete) graft loss.[5] Long-term maintenance of islet graft function will be central to islet transplantation becoming a viable treatment option for T1D patients.

Patient and methods

A 35-year-old, Non-Hispanic white female with situs inversus and a 26-year history of T1D complicated by hypoglycemia unawareness and resultant severe hypoglycemic events received an islet transplant at the University of Illinois at Chicago (UIC) Hospital (consent obtained under Institutional Research Board approval 2004-0532). In the months prior to transplant, she was experiencing approximately four episodes per week of blood glucose <3.1 mmol/L, the majority of times without symptoms, and within the nine months prior to her transplant she had a severe hypoglycemic event that required EMS intervention, therefore meeting inclusion criteria for the UIC clinical trial (NCT00679041). The patient's HbA1c at the time of transplant was 50 mmol/mol (6.7%) and she was

requiring 0.5–0.7 units of insulin per kilogram weight per day (U/kg/day) via subcutaneous pump. The patient's other medical history included: a right partial thyroidectomy for follicular adenoma sixteen years prior to transplant; a left vitrectomy eight years before transplant; and subsequent surgical treatment for both glaucoma and a cataract in the same eye three years prior to transplant. Additionally, four years before transplant, the patient had an episode of idiopathic pancreatitis. The patient was CMV and EBV positive prior to transplant.

Regarding the islet isolation, the pancreas donor was a 60-year-old woman, weighing 98 kg (BMI of 34.9), who died of a stroke after approximately a four-day hospital stay. The donor was CMV and EBV positive. The pancreatic cold ischemia time was six hours, two minutes. The islet isolation was performed at UIC's islet isolation facility, using Liberase (lot# 93456920, Roche, Basel, CH) according to the UIC isolation protocol,[6] and yielded a total of 387,092 islet equivalents (IEq), with a viability of 90%, and a glucose stimulation insulin secretion (GSIS) index of 3.5. At transplant, the patient weighed 58.6 kg and thus received an islet dose of 6,606 IEq/kg; the total transplanted tissue volume was 5.5 mL. Because of her situs inversus, an ultrasound vein mapping was performed pre-transplant to visualize the hepatic vasculature. There were minor vascular access difficulties noted, attributed to the unique anatomy of her situs inversus, but only one venous puncture was performed.

The post-transplant hospital course was notable for minor pulmonary sub-segmental atelectasis, as well as the development of a relatively large hepatic hematoma (9 × 12 cm). The patient remained hospitalized for eight days following transplant for monitoring of the hepatic hematoma, as well as management of both pain and significant nausea and vomiting. The patient completed the standard seven day course of prophylactic enoxaparin sodium (Lovenox, Sanofi, Paris, FR) following transplant, with no increase in the hematoma size. Approximately two months after transplant, the patient fell, striking her abdomen. As her hemoglobin after the fall was 64 g/L (down from 81 g/L the week before), the patient was hospitalized to rule out a new traumatic intra-hepatic bleed (a slight increase to 13 × 11 cm was seen), and for transfusion of three units of blood. The hematoma gradually resolved over the next 11 months, decreasing to a final size of 3.7 × 3 cm.

Results

After receiving the islet cell transplant, the patient had no further episodes of severe hypoglycemia, and the episodes of asymptomatic hypoglycemia (not meeting criteria for severe) tapered to almost none. The patient developed several additional medical conditions over the years as well. One year following transplant, due to concerning abnormalities seen on ultrasound, the patient had a completion right thyroidectomy. Pathologic examination found papillary carcinoma, as well as a follicular adenoma. Four years following transplant, the patient had a cholecystectomy due to chronic cholecystitis. Throughout follow-up, the patient has not developed any opportunistic infections.

The patient's induction immunosuppression regimen included etanercept (50 mg pre-transplant and 25 mg on days 3, 7, and 10 post-transplant; Enbrel, Amgen, Thousand Oaks, CA) and daclizumab (150 mg IV every 4 weeks; Zenapax, Roche, Basel, CH). The patient's maintenance immunosuppression included tacrolimus (Prograf, Astellas, Tokyo, JP) with targeted trough levels of 3–6 ng/mL throughout the study, and sirolimus (Rapamune, Pfizer, New York, NY) with targeted trough levels of 10–15 ng/mL for the first three months post-transplant, then 7–10 ng/mL thereafter. Two years following transplant, the patient had an anaphylactoid reaction to daclizumab, which was then immediately discontinued. Due to persistent oral ulcers, sirolimus was also switched to mycophenolate mofetil 1000 mg twice daily (CellCept, Genentech, South San Francisco, CA), then switched to mycophenolic acid (Myfortic, Novartis, Basel, CH) at 720 mg twice daily five years post-transplant. The patient is currently on a regimen of tacrolimus and mycophenolic acid at 1 mg twice daily and 720 mg twice daily, respectively.

The patient had 0% panel reactive antibodies (PRA), and was negative for anti-GAD65, anti-ICA, and anti-IA2 antibodies prior to transplant. Since transplant, the patient has not developed any PRA (remains at 0%). However at year two, anti-insulin antibodies developed at >50 IU/mL, which have remained at ~40 IU/mL since. At year three post-transplant, anti-GAD antibodies increased to
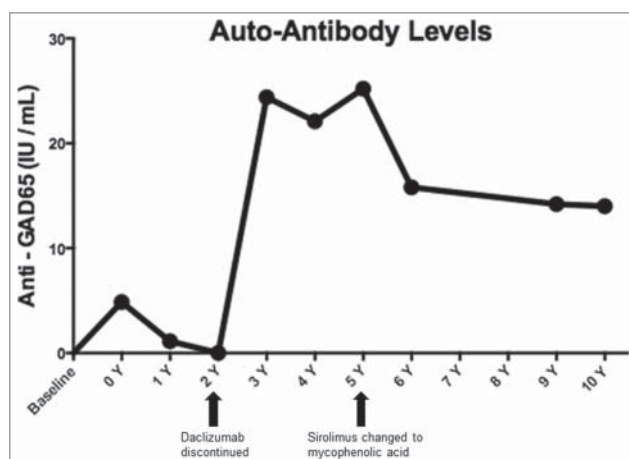
Figure 1. Anti-GAD65 autoantibody levels over 10 year follow-up.

~24 IU/mL through year six, and then decreased (Figure 1; arrows represent change in immunosuppression noted above). Anti-ICA and anti-IA2 antibodies remained negative throughout follow-up.

In the first days following transplant, the patient required 8 units per day (U/d) of insulin glargine (Lantus, Sanofi, Paris, FR). Ten days after transplant, the dose was reduced to 4 U/d. Approximately two months after transplant, the patient became insulin independent. As part of the UIC protocol, the patient was on exenatide (Byetta, AstraZeneca, London, UK) from 5–10 μg twice a day intermittently until ten weeks following the transplant, when it was discontinued due to severe intolerance with intractable nausea and vomiting. The patient was started on sitagliptin (Januvia, Merck, Kenilworth, NJ) 100 mg daily two years following transplant to help improve glycemic control, and during years 2–3 post-transplant the patient intermittently required low dose (~4 U/month) insulin aspart (Novolog, Novo Nordisk, Bagsværd, DK) for occasional high fasting glucose readings, but since that time she has again been insulin independent. The 10-year glycemic and HbA1c profiles (Figure 2) show that the patient maintained normal fasting blood glucose levels at ~5.5 mmol/L and HbA1c levels between 40 and 51 mmol/mol (5.8% – 6.8%).

To monitor graft function, metabolic tests were performed periodically over the 10 years including: the oral glucose tolerance test, the intravenous glucose tolerance test, the mixed meal test, and the glucagon stimulation test. As shown in Figure 3, the transplanted islet graft consistently produced detectable fasting C-peptide levels which then appropriately increased in response to glucose/glucagon stimulation during metabolic testing over the 10 years following transplant. Figure 4 depicts the insulin and glucose responses from the individual metabolic tests conducted at 10-years of insulin independence, with appropriate responses to glucose/glucagon stimulation in all cases (see Figure 3 for corresponding C-peptide levels at 10-years). Figures 3 & 4 graphically illustrate the ongoing islet graft function.

Despite the long-term use of immunosuppression, which can potentially have nephrotoxic effects, the patient's creatinine post-transplantation remained stable and normal (Figure 5A). In addition, the patient's overall cardiovascular risk profile improved over time as indicated by regression of carotid intima-media thickness (CIMT), specifically the common carotid artery (Figure 5B).

Discussion

This short report describes a patient achieving more than ten years of insulin independence following a single low mass islet cell transplant. A recent study reported a median duration of insulin independence after a single islet transplant (mean 7459 IEq/kg) of 11.3 months.[7] It is notable that the current patient received an approximately similar islet mass of only 6,606 IEq/kg and has remained insulin independent for over 10 years. It is currently thought that 9,000-10,000 IEq/kg (over multiple transplants) is required to attain insulin independence.[8] After transplant, the patient has consistently displayed substantial improvement in glycemic control, insulin independence, and islet graft function as indicated by metabolic testing. While the patient's HbA1c was relatively low prior to transplant, the Diabetes Control and Complications Trial has clearly established the benefits of lowering HbA1c as close to normal as possible, with a reduction in both incidence and progression of long-term complications.[9]

Success of islet transplantation is based on both donor and recipient factors. In this case the donor was a female, with highly potent islets as evident by a GSIS value >3, both factors that have been previously associated with enhanced islet transplant success.[3,10] In contrast, the donor's older age potentially resulted in a lower quantity of islets isolated, resulting in 6,606 IEq/kg for the recipient, which is less than the currently recommended infusion amount. In addition, pancreata from donors where the cause of death is non-traumatic
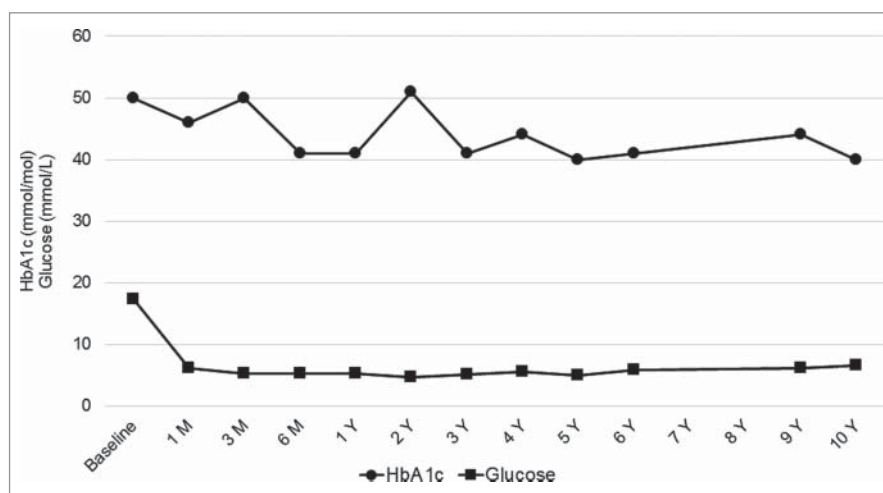
Figure 2. HbA1c and fasting blood glucose levels over 10 year follow-up.

(as in this case) yield a lower beta-cell mass for the recipient than donors where the cause of death is trauma.[11] Furthermore, certain recipient factors are integral to long-term graft success. For example, this patient only required 0.6 U/kg/day insulin on average prior to transplant indicating the patient was insulin sensitive. Moreover, the patient had a favorable immune profile for islet transplant. She had ~0% panel reactive antibodies, as well as being negative for anti-GAD65, anti-ICA, and anti-IA2 prior to transplant.

In general, transplant patients receive intense induction immunosuppression immediately post-transplant, followed by a less intense maintenance regimen.[12] This patient was maintained on IL-2 receptor blockade (daclizumab) for two years to reduce the risk of rejection while maintaining relatively low target trough levels of tacrolimus. Interestingly, after cessation of daclizumab, the patient presented with de novo anti-insulin (year two) and anti-GAD65 autoantibodies (year three, Figure 1) and worsening glycemic
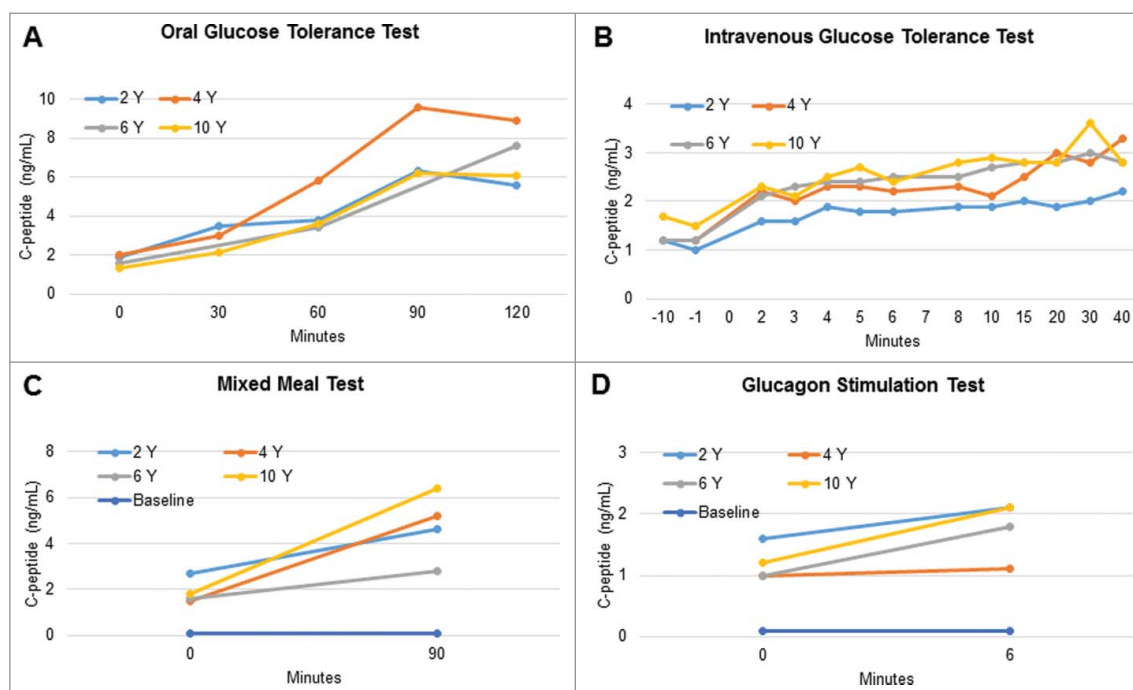

Figure 3. C-Peptide levels obtained during metabolic testing over 10-year follow up. (A): Oral Glucose Tolerance Test. (B): Intravenous Glucose Tolerance Test. (C): Mixed Meal Test. (D): Glucagon Stimulation Test.
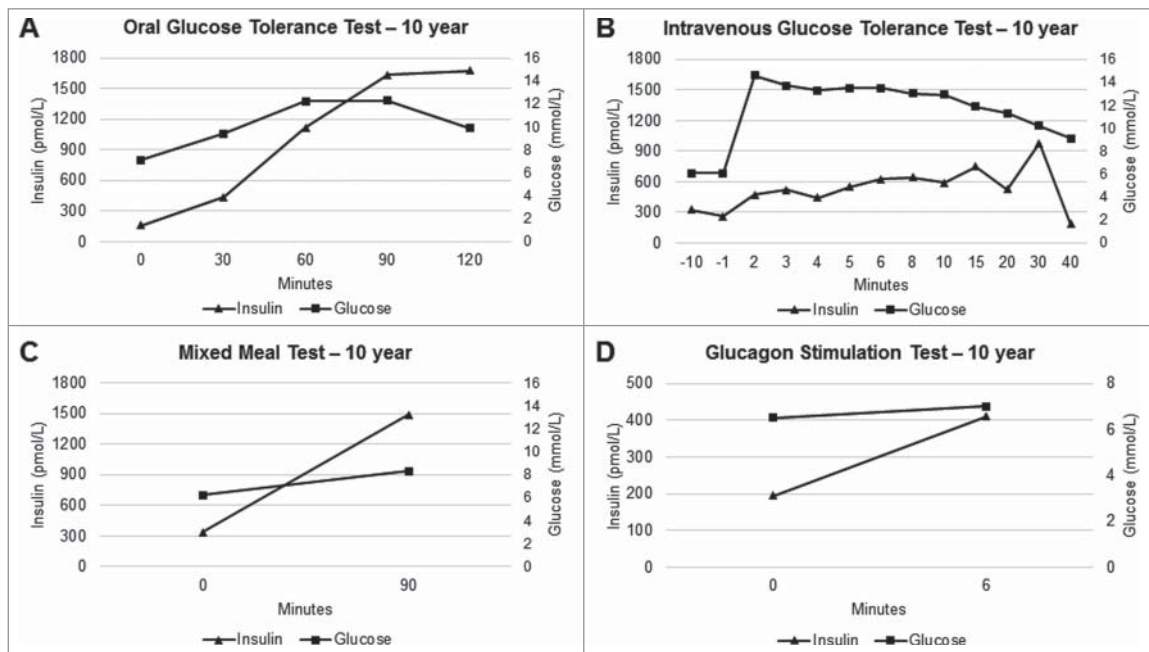
Figure 4. Insulin and glucose levels from metabolic testing at 10 years (see Figure 2 for corresponding C-peptide levels). (A): Oral Glucose Tolerance Test. (B): Intravenous Glucose Tolerance Test. (C): Mixed Meal Test. (D): Glucagon Stimulation Test.

control (Figure 2). A prior study has shown that the development of new autoantibodies after transplant is associated with significantly lower graft survival.[13] Due to this development of T1D autoimmunity, target tacrolimus trough levels were increased from 3–6 ng/mL to 5–7 ng/mL. Subsequently, glycemic control improved, despite persistently elevated autoantibodies. The remarkable duration of graft function with the prolonged use of daclizumab is unique,[14] when several prior studies have found T-cell depleting immunosuppression to be associated with more durable graft function.[15] The patient also received etanercept as part of the immunosuppression regimen, which has

been shown to be associated with higher rates of insulin independence,[15] and exenatide, which is unique to the UIC Protocol,[4] both of which may have played a role in the patient's excellent graft function.

This case highlights the challenges in the field of islet cell transplantation: inter-individual variability in outcomes and limited predictors of success.[3] Some patients achieve long-term insulin independence with an unexceptional islet preparation, while other patients never achieve euglycemia despite multiple islet cell transplants. Because of this patient's frequent clinical visits following transplant, she received highly personalized care, which likely contributed to her
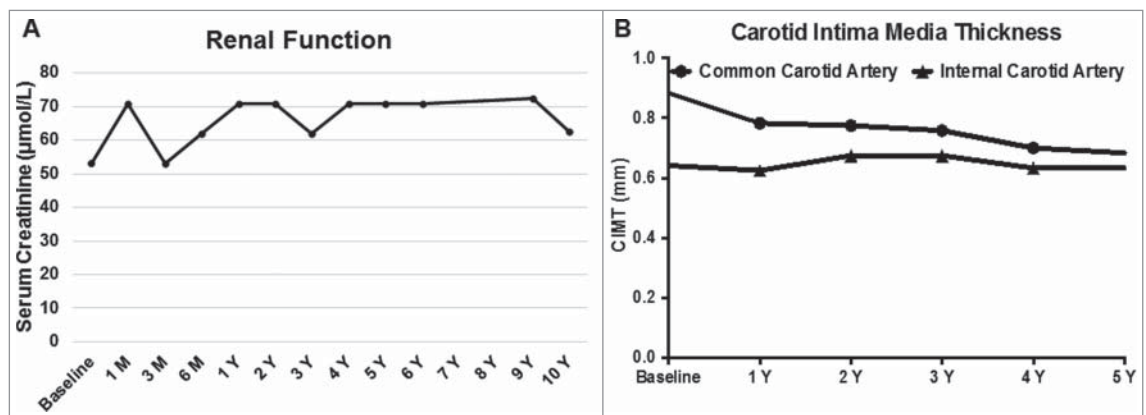

Figure 5. Renal function and carotid intima-media thickness over 10 year follow-up. (A): Serum creatinine level. (B): Carotid intima-media thickness of the common and internal carotid arteries.

prolonged insulin independence. Additionally, characteristics of the islets (e.g., potency) and recipient (e.g., low insulin requirement pre-transplant, zero PRA) were present that have been associated with better long term graft function. The use of etanercept, and possibly exenatide, and prolonged, non-T-cell depleting immunosuppression may also have played a role in the patient's long-term graft function. Conversely, long-term function has occurred despite a low transplanted islet mass, a post-infusion liver hematoma, the lack of T-cell depleting antibody induction, and the development of de novo anti-insulin and anti-GAD65 autoantibodies after islet transplant. The patient has continued to maintain remarkable insulin independence and glycemic control more than 10 years after a single islet cell infusion, however no definitive conclusions can be made from this case with regards to donor, recipient or transplant characteristics predictive of transplant success.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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