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COMBINED PANCREATIC ISLET AND KIDNEY TRANSPLANTATION IN A CHILD WITH UNSTABLE TYPE 1 DIABETES AND END-STAGE RENAL DISEASE

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Abstract

Islet transplantation after successful kidney transplantation is a recognized treatment for adults with diabetes and end-stage renal disease (ESRD), but has not been considered an option in the pediatric population. To our knowledge, we report the first combined islet and kidney transplant in a child. The patient was born with bilateral renal hypoplasia and was diagnosed with type 1 diabetes mellitus at age 13 months. He had erratic glycemic control and hypoglycemia unawareness. At 6 years of age, the child safely underwent simultaneous islet and live donor kidney transplantation. Although function of the islet graft was transient, the combined transplant provided significant benefits in terms of glucose control and overall growth and development. Such an approach represents a viable treatment option for pediatric patients with ESRD and unstable diabetes.

Keywords

Islet transplantation; Pediatric; Renal disease; Kidney transplantation; Type I diabetes

INTRODUCTION

Pancreatic islet transplantation is a promising therapy for adults with type 1 diabetes mellitus (T1DM). In children with T1DM, however, islet transplantation is not considered a treatment option due to the risks associated with the procedure and the potential for renal impairment and malignancy associated with long-term immunosuppression. In this report, we describe the first case of a combined islet/kidney transplant in a 6 year old boy with ESRD and T1DM. This patient was thought to be a suitable candidate for the combined

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procedure for two reasons. First, due to the child's small size, the kidney was to be implanted intraperitoneally which would permit infusion of the islets into the portal vein during the kidney transplant procedure. Second, the child would receive induction and maintenance immunosuppression for the renal allograft and thus would not require additional immunosuppression for the islet transplant.

CASE HISTORY

The patient was diagnosed with bilateral renal hypoplasia and severe renal insufficiency shortly after birth. His condition was complicated by global developmental delay, choreoathetoid movements, oral motor dysfunction, esophageal reflux, persistent vomiting, and growth failure despite an aggressive gastric tube feeding regimen. At 13 months of age, he developed diabetic ketoacidosis and was diagnosed with T1DM. Autoantibodies against insulin, islets, and tyrosine kinase IA-2 were positive, and c-peptide levels were undetectable. Management of his diabetes was especially challenging because of his young age, neurological symptoms and feeding difficulties. Insulin pump therapy was not an option because of his developmental delay and choreoathetoid movements.

At the time of transplant, the patient weighed 18.5 kg (< 5th percentile for age), and had an estimated glomerular filtration rate (eGFR) of 9 ml/min/1.73 m^2 (1). He was receiving insulin at a mean total dose of 1.0 unit/kg/day, and his hemoglobin A1c (HbA1c) ranged from 7.3% to 9.4%. Despite a structured feeding regimen that included formula feeds, glycemic control was characterized by wide excursions in plasma glucose levels, frequent hypoglycemia, and hypoglycemic unawareness. For these reasons, he was considered a suitable candidate for a combined kidney and pancreatic islet transplant, which was approved by the Institutional Review Board at UCSF (approval #: H8204-19640) and performed in accordance with our institutional islet and kidney transplant protocols.

Islets were obtained from a 40 year old female deceased donor with a history of migraine headaches and tobacco use, but no history of diabetes. Her BMI was 42, and HbA1c was 5.5% at the time of donation. The islets were isolated using a modification of the automated Ricordi method and maintained in culture for 48 hours (2,3). A total of 557,000 islet equivalents (IEQ) were available for infusion. The high purity islet preparation contained 381,000 IEQ in a settled volume of 1.3cc, was 90% pure, and had a viability of 98%. The lower purity fraction contained 176,000 IEQ in a settled volume of 4.5cc, was 55% pure, and had a viability of 98%. The glucose stimulated insulin release (GSIR) index for the preparation was 3.4, and the endotoxin level was < 1.1EU/kg. When the islets were ready for infusion, live donor kidney transplant was performed, with the patient's mother being the donor. After the renal allograft was implanted into the child's abdomen, the portal vein was cannulated and the islets were infused. Portal venous pressure was 12 mmHg before infusion, and rose to a peak of 20 mmHg near the end of the procedure, at which point the infusion was stopped. The patient received an estimated 450,000 IEQ (approximately 80% of the total number) corresponding to 24,324 IEQ/kg body weight (4). Heparin (50 units/kg) was administered intravenously during the islet infusion and for 72 hours afterwards. Enoxaparin injections were then given for seven days, after which oral/G-tube aspirin (81 mg/day) was initiated. There were no surgical complications.

Induction immunosuppression consisted of anti-thymocyte globulin (5 mg/kg) with methylprednisolone (0.5 mg/kg) given as a premedication. In addition, daclizumab (1 mg/kg) was given one day before transplant and at weeks 4, 6, 8, 11 and months 4, 5, and 6 after transplant. At our institution, standard induction immunosuppression for kidney transplant in unsensitized patients is daclizumab. Thymoglobulin was added as adjunctive therapy to ensure adequate immunosuppression for the islet transplant. Maintenance immunosuppression consisted of mycophenolate mofetil (600 mg/m^2/day) and tacrolimus. Tacrolimus target trough levels were 8–10 μg/L for the first 12 weeks after transplant, then 5–7 μg/L until three years post-transplant and 3–5 μg/L thereafter. These levels were selected to minimize toxicity to the kidney and islet grafts.

Glycemic control was achieved with intravenous insulin for the first 10 days after transplant, after which insulin glargine was given subcutaneously to maintain fasting blood glucose levels <140 mg/dL and post-prandial levels <180 mg/dL At the time of discharge one month post-transplant, the patient required approximately 10% of his pre-transplant insulin dose. At five months post-transplant, he was successfully weaned off insulin and remained insulin independent for approximately two months. Fasting and stimulated c-peptide measurements confirmed beta cell function (1.58 ng/mL and 3.42 ng/mL, respectively).

Seven months post-transplant, the patient's blood glucose levels began to increase. Due to concerns about possible rejection, anti-thymocyte globulin (3 mg/kg) was administered. Islet function did not improve, and insulin was restarted at approximately 60% of his pre-transplant dose. Thereafter, insulin requirements slowly increased, and by 15 months post-transplant, full insulin replacement was required. C-peptide measurements and mixed meal tolerance tests were consistent with declining beta cell function (5). At 24 months post-transplant, a stimulated c-peptide level was <0.1 ng/ml, showing complete loss of islet function. (Figure 1)

The post-transplant period was notable for significant progress in growth velocity, which increased from 2 cm/year before transplant to 11 cm/year at 12 months after transplant. In addition, choreoathetoid movements decreased significantly within six months post-transplant, and ataxia completely resolved. Presently, the patient remains on a stable caloric regimen via gastrostomy tube feeds, with stable glucose control.

Surveillance kidney biopsies performed at three and 12 months after transplant showed no abnormalities. A kidney biopsy performed at 23 months post-transplant to evaluate an increase in serum creatinine showed no evidence of rejection. A second for-cause biopsy performed at 31 months post-transplant was consistent with borderline cellular rejection but no antibody-mediated rejection, and mycophenolate mofetil was increased with subsequent improvement in creatinine.(6). Since then, the eGFR has been stable at approximately 80 ml/min/1.73 m^2.

Pre-transplant HLA typing showed a 3/6 match with the kidney donor and a 1/6 match (DR) with the islet donor. Class I and II panel reactive antibody (PRA) levels were zero. Donor specific antibody testing performed at the time of suspected islet rejection (7 months after transplant) did not detect antibodies to either the islet or kidney donor. However, by 12

months after transplant, class II anti-HLA antibodies specific to both the islet and kidney donors were detected (Figure 3). At this time, c-peptide levels were declining, and the patient's insulin requirements were increasing. The patient had detectable autoantibodies to ICA512 and microinsulin (mIAA) prior to transplant. Their levels did not change significantly when measured at 90, 180, and 365 days after transplant.

DISCUSSION

We describe a 6 year old boy with congenital renal hypoplasia and T1DM who received a simultaneous living donor kidney and deceased donor islet transplant. Complete, albeit transient insulin independence was achieved at months 5–7 post-transplant. Although the patient subsequently lost islet function and resumed full insulin therapy, blood glycemic control is improved and hypoglycemic episodes are rare.

In this child, achieving glycemic control was challenging due to unpredictability in his activity levels and multiple daily episodes of emesis resulting in an imbalance between his insulin dosing and carbohydrate intake. These issues were exacerbated by significant developmental delay and inability to communicate symptoms of high or low blood sugar. A combined kidney and whole pancreas transplant was not an option given the small body size; however, a combined kidney and islet transplant was considered reasonable. The possibility of simultaneous islet and kidney transplantation from a deceased donor was considered, as this could improve immune monitoring of the graft. We ultimately chose the live donor approach because it allowed the timely transplantation of a high quality kidney with a favorable immunologic match between donor and recipient.

The patient's glycemic stability improved immediately after transplant, as evidenced by the decrease in the frequency of severe hypoglycemic episodes from multiple daily events to approximately 1–2 per month. This improvement has persisted despite the gradual loss of islet graft function, and he continues to be essentially free of severe hypoglycemic episodes. HbA1c levels improved after transplant, with values decreasing from 7.3% in the setting of daily hypoglycemia before transplant, to 5.9% one year post-transplant despite a concomitant decrease in the frequency of hypoglycemia (Figure 1).

Although c-peptide has declined to undetectable levels, the patient continues to require less insulin after the transplant than before the transplant (Figure 1). The patient's reduced insulin needs as he has aged are not typical of T1DM in children, where insulin requirements usually increase with age due to decreasing insulin sensitivity. This improvement in sensitivity may in part be explained by the increase in renal function after transplant. In both human and animal models, chronic kidney disease is associated with significant insulin resistance which improves after normalization of renal function (7–9). In addition, it is likely that the patient's improved feeding tolerance and better overall growth and development after transplant has made long-term glucose control relatively easier.

The number of islets infused into this child was significantly greater than is usually needed to render adult islet recipients insulin independent, and the viability and GSIR index of the preparation show that these were high quality islets (4). Despite this, the patient achieved

only a brief period of insulin independence and eventually lost all islet function. It is possible that initial engraftment was poor, and only a relatively small fraction of the inoculum survived. Engraftment may have been compromised by the small size of the liver and resultant reduced volume of distribution. In addition, the patient did not receive the anti-inflammatory agent etanercept, a tumor necrosis factor-alpha antagonist, since it was not being used at our institution during that time (10,11). This may have exacerbated the early destruction of the islets by the immediate blood-mediated inflammatory response which is known to destroy a significant fraction of the islet mass soon after infusion (12). Survival of the islet graft may also have been compromised by allo- and autoimmune processes, particularly since relatively low tacrolimus trough levels were maintained. Anti-HLA antibodies to both the islet and kidney donors were first detected at approximately 12 months post-transplant and islet function began to decline during this same time period, suggesting that ongoing immune destruction of the islet cells was occurring (Figure 3) (13,14).

In summary, although function of the islets was transient, the combined islet-kidney transplant provided several benefits to this child, including improved nutrition and enhanced quality of life. We demonstrate that a combined islet-kidney transplant in a small child is safe, feasible, and can significantly reduce life-threatening hypoglycemic events. Such an approach represents a viable therapeutic option for selected pediatric and adult patients with end-stage renal disease and unstable diabetes, and may also be applicable to diabetic patients undergoing transplantation of other organs.

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Abbreviations

ESRD	end stage renal disease
T1DM	Type1 diabetes mellitus
eGFR	estimated Glomerular Filtration Rate
HbA1c	hemoglobin A1c
BID	twice daily
IEQ	islet equivalents
GSIR	Glucose stimulated insulin release
MMF	mycophenolate mofetil
PRA	panel of reactive antibody

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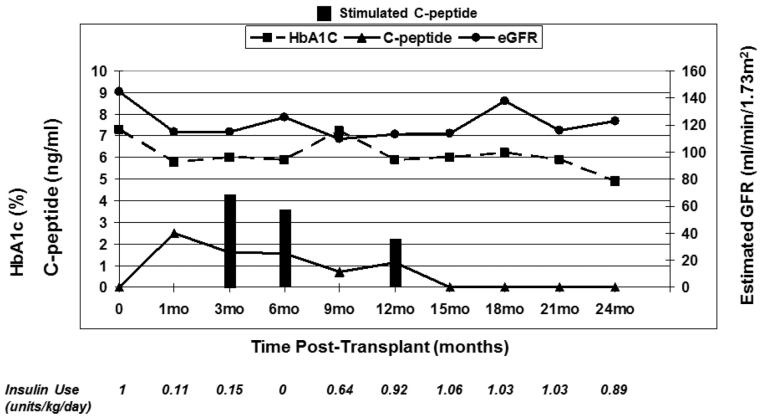

Figure 1. Islet and kidney function after combined transplantation

The patient became insulin independent during months 5–7 after transplant and resumed full dose insulin use by 12 months. The bars represent stimulated c-peptide levels obtained during mixed meal tolerance tests performed at 3, 6, and 12 months post-transplant. Fasting c-peptide levels remained detectable through 12 months post-transplant but became undetectable (<0.1 ng/ml) by 15 months post-transplant.

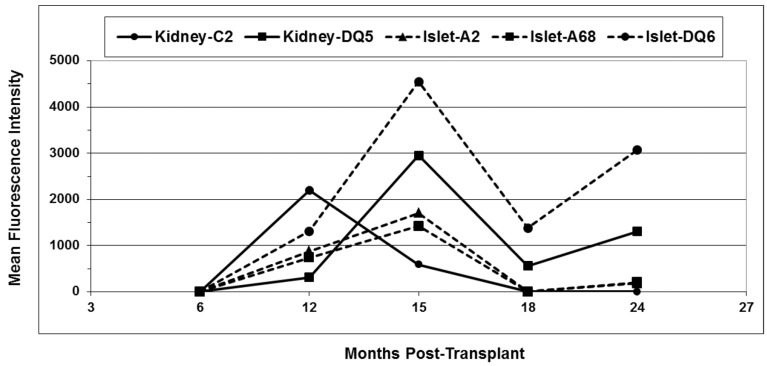

Figure 2. Development of donor-specific antibodies after combined islet-kidney transplantation

Antibodies to the kidney (solid lines) and islet (dashed lines) donor HLA types are depicted. The increases in anti-islet antibodies correlated with loss of islet graft function. The increase in antibodies to DQ5 from the kidney donor seen at the same time points is most likely due to cross reactivity between anti-DQ5 and anti-DQ6 antibodies since DQ5 and DQ6 share many epitopes. Mean fluorescence intensity (MFI) level cutoffs at our institution are as follows: high risk: >8500; moderate risk: 2000–8499; low risk: 1000–1999.