Islet Transplants and Impact on Secondary Diabetic Complications: Does C-Peptide Protect the Kidney?

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With successful reversal of chemical diabetes over 30 yr ago in rodents, islet transplantation entered the realm of clinical possibility. (1–4) Early attempts to replicate rodent studies in patients were fraught with difficulty — compound by poor quality, low yield islet preparations, and ineffective immunosuppression.

Introduction of the Ricordi chamber for controlled mechanical and enzymatic pancreatic dissociation in 1986 led to major improvements in quality and yield isolation of human islets (5,6). The impact of this new method for islet isolation rapidly bore fruit: within four years, the first clinical successes began to emerge—most remarkable of which was a series of patients with surgical diabetes resulting from abdominal exenteration in which half of the treated subjects were able to maintain insulin independence after islet transplantation (7,8). Introduction of a more consistent collagenase enzyme for pancreatic digestion (Liberase) (9,10), techniques for controlled enzymatic perfusion of the pancreatic duct (11), use of a cooled COBE cell apheresis system (12), and less toxic osmotic gradients for rapid islet purification (13,14) transformed methods for islet isolation from art to science, paving the way for more intensive clinical efforts. Development of standardized procedures, stringent islet product release criteria, and upgrading of islet isolation facilities to meet cGMP standards have recently provided a much improved and ultra-clean islet product for safer implantation into patients (15).

A series of refinements in peritransplant management introduced by the Giessen and Milan groups led to success rates of 50% in patients with type 1 diabetes in these centers (13,16), but overall outcomes in over 450 patients documented in the International Registry remained dismal, with only 8% of patients maintaining insulin independence (17). As islet transplantation moved into the new millennium, further refinements in the so-called Edmonton Protocol led to dramatic improvements in clinical outcome, with all of the first seven patients remaining insulin-free now beyond 4 yr (18). Expanded numbers with more prolonged follow-up from the Edmonton group now confirm 1-yr insulin independence rates of 80% (19) and 3-yr islet graft function rates of close to 90% (based on persistent C-peptide function), and two of the initial three patients remain insulin-free now beyond 4 yr (20). Preliminary results from a nine-center international Immune Tolerance Network trial (21) and data accruing from over 250 patients in more than 25 additional active centers further justify the gradual transition of status for islet transplantation from research to standard practice of medicine for patients with unstable forms of type 1 diabetes who have failed on intensive insulin therapy.

A number of key further refinements have further enhanced the success of islet transplantation over the past 3 yr. The two-layer oxygenated perfluorodecalin (PFC) system for pancreas protection during transportation initially developed by Kuroda and colleagues (22) and subsequent introduction into clinical practice by Hering and colleagues (23) has now been widely adopted with major positive impact on islet viability and yield (24–26). Further recent refinements in islet culture protocols, largely based on media supplements with insulin-transferrin-selenium (ITS) as initially described by Fraga et al. (27,28), have improved both the safety and the practicality of islet transplantation by: (a) improving islet purity through reduction in exocrine contamination (29); (b) lowering transplant tissue volume and therefore potential for elevated portal pressure or portal thrombosis (30); (c) avoiding a need for transplant recipients to relocate to the transplant center ahead of transplantation; and (d) facilitating islet shipment between regional islet isolation and remote transplant centers (31). The introduction of the bag technique for gravity infusion of islets by the Miami group has allowed for continuous monitoring of portal pressure during islet infusion, possibly reducing the risk of portal thrombosis, and has further improved sterility by avoiding contamination of islet preparations within the radiology department.

Hering et al. have integrated a number of important steps including: PFC pancreas transportation; careful donor and recipient selection; a new iodixanol non-ficoll based purification gradient; islet culture; thymoglobulin and anti-TNFα (etanercept) induction; less diabetogenic, calcineurin inhibitor-free maintenance immune suppression; and intensive insulin and intravenous heparin in the peri-transplant period (32). Attention to detail every step of the way led to insulin independence after single donor islet infusions in the first eight recipients,
with five of eight maintaining insulin independence in the longer term (32).

With such remarkable progress over the past three years, it is clear that islet transplantation can provide a level of glycemic control that far exceeds intensive insulin or pump therapy (19). Provided rejection and autoimmune recurrence can be prevented by non-diabetogenic but potent antirejection drugs, glycated HbA1C can remain within the normal range, and emerging outcomes in islet transplantation may soon parallel the results in whole pancreas transplantation, but with less potential risk of peri-transplant morbidity.

However, robust data has yet to emerge on the impact of successful islet transplantation in improved longevity or protection against secondary complications of diabetes (33). The studies of Fioretto et al. (34) showed that up to 10 yr of excellent metabolic control were required in non-uremic recipients of whole pancreas transplants to show stabilization and reversal of diabetic lesions in the native kidney. It seems more than likely that successful islet grafts will have a similar positive impact on diabetic renal lesions and will protect against neuropathy and vasculopathy, but only time (and carefully controlled studies) will tell.

The report by Fiorina et al. (35) in this issue of the Journal of the American Society of Nephrology is therefore both timely and important. The Milan group have shown for the first time that patients with persistent islet function after islet-kidney transplantation have significant improved survival of their renal allografts (83% versus 51% in controls at 7 yr) (35). The Milan group has demonstrated an impressive rate of insulin independence with steroid- and cyclosporine-based therapy, even though this is currently no longer in vogue for islet transplantation, demonstrating excellent potency of their islet preparations. They have shown a clear association between renal graft function and islet survival, with positive C-peptide secretion (>0.5 ng/ml) linked to improved kidney survival and reduced albumin excretion even in non-insulin-independent subjects. Interestingly, HbA1C levels were comparable in both groups, making it hard to implicate improved metabolic function with improved renal allograft survival. Could this be further evidence for a therapeutic role of C-peptide per se as an active protective factor for the diabetic kidney? C-peptide was previously thought to possess no biologic activity and was an inactive byproduct of insulin release. Several recent studies however have shown that administration of C-peptide to patients with type 1 diabetes can improve renal function, reduce albumin excretion, prevent glomerular hyperfiltration, improve glucose clearance, and improve autonomic nerve function (36,37). Fiorina et al. have shown increased activity of Na\(^+\)-K\(^+\)-ATPase in both peripheral blood red cells and in renal biopsy material, which is entirely consistent with previously described pathways for the C-peptide effect through stimulation of endothelial nitric oxide synthase (38,39).

One potential confounding bias in the Milan study is that patients who reject their islet grafts and become C-peptide-negative could also be more immunologically susceptible to both acute and chronic rejection. Larger, controlled studies will be needed to define this more precisely.

These are indeed exciting times, as cellular replacement therapy for diabetes evolves as an alternative therapy to insulin. Prospects on the horizon include further refinements in single donor islet transplant protocols, living donor laparoscopic distal pancreatectomy to expand the donor pool, inclusion of children in newer minimal immunosuppression and tolerance protocols, and ultimately use of xenogeneic or stem cell sources to match the ever-expanding burden of diabetes.

References