Islet Transplantation for Type 1 Diabetes, 2015: What Have We Learned From Alloislet and Autoislet Successes?

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The therapeutic potential of pancreatic islet allotransplantation, in which human donor islets are used, as a treatment for type 1 diabetes (T1D) has fascinated diabetes researchers and clinicians for decades. At the same time, the therapeutic potential of total pancreatectomy and islet autotransplantation (TPIAT) (in which one's own islets are used) as a preventive treatment for diabetes in patients who undergo total pancreatectomy for chronic, painful pancreatitis has received relatively less attention. This is ironic, since the latter has been much more effective than the former in terms of successful glucose management and duration of efficacy. The reasons for this disparity can be partially identified. TPIAT receives very little attention in textbooks of internal medicine and general surgery and surprisingly little print in textbooks of endocrinology and transplantation. T1D is much more predominant than TPIAT as a clinical entity. Provision of insulin or replacement of islets is mandatory and a primary goal in T1D. Provision of pain relief from chronic pancreatitis is the primary goal of total pancreatectomy in TPIAT, whereas treatment of diabetes, and certainly prevention of diabetes, has been more of a secondary consideration. Nonetheless, research developments in both fields have contributed to success in one another. In this Perspective, I will provide a brief history of islet transplantation and contrast and compare the procedures of allo- and autoislet transplantation from three major points of view *1*) the procedures of islet procurement, isolation, and transplantation; *2*) the role and complications of immunosuppressive drugs; and *3*) the posttransplant consequences on β- as well as α-cell function.

BRIEF HISTORY

Although success with both allo- and autoislet transplantation in humans began in 1978–1980 (1,2), the first attempt can be traced back to 1894. Williams described the use of sheep pancreas and extracts of pancreas for oral and subcutaneous therapy for diabetes and reported overt failures (3). Much later, in the 1980s, many groups experimented with various approaches to alloislet transplantation in humans, primarily those with type 1 diabetes (T1D) (4–17), and reported outcomes that gave rise to optimism. The experimental groups were small, and the numbers of islets transplanted were variable; in all instances, varying degrees of success were reported ranging from 22 days to 6 years. On the other hand, in 1995 it was reported

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that the success rate for islet autotransplantation at 2 years postpancreatectomy was 70% in those patients receiving >300,000 islets (18). The main predictor of success was the number of islets transplanted. By 2000, the Edmonton group (19) reported a posttransplant success rate of 100% in a group of seven T1D recipients of allotransplantation, six of whom underwent two transplant procedures and one of whom received three. The average total islet mass transplanted was 11,547 ± 1,604 islet equivalents/kg body wt, with a median posttransplant follow-up of 11.9 months (range 4.4–14.9). However, 5 years later the Edmonton group (20) reported less dramatic results. By 2005, a total of 65 T1D patients had been transplanted, of whom 10% were insulin independent, 80% were C-peptide positive but using insulin, and 10% were C-peptide negative and using insulin. More recently, reports of alloislet transplantation have been more encouraging (21–25).

In 2012, Sutherland et al. (26) reported the rates of success (defined as HbA_{1c} levels <7.0%, C-peptide positivity, and use of minimal insulin at bedtime) in 409 recipients of islet autotransplantation. At 3 years posttransplant, 30% were insulin independent and 33% had partial function (C-peptide positive and once-daily use of insulin). Once again, success rates correlated with islet yield, i.e., islet yields of 2,500/kg, 2,501–5,000 islets/kg, and >5,000 islets/kg yielded insulin independence rates of 12, 22, and 72%, respectively, and partial success of 33, 62, and 24%, respectively. These outcomes are consistent with the autoislet success rates in another large series reported by Clayton et al. (27). While outstripping alloislet success rates, the autoislet data optimistically point to the realistic possibility that success rates for alloislets will similarly increase as improvements are made in alloislet procurement, immunosuppressive regimens, and transplant site selection.

ALLO VERSUS AUTO: DIFFERENCES IN ISLET PROCUREMENT, ISOLATION, AND TRANSPLANTATION

There are major differences between the processes of procurement and isolation of islets in the allo- and autoislet transplantation scenarios. As with whole pancreas transplantation, pancreases procured for alloislet transplantation are donations from people who have sustained acute and lethal physical or medical injury. The donor is maintained under life support conditions until a pronouncement of brain death is made. Thereafter, a surgical team removes multiple donated organs for transportation to often distant transplant sites. A great deal of variety exists in the timing and conditions of the removed organs depending on the surgical team's priorities regarding which organ has a higher priority for the intended recipients. This creates an important variable in the ultimate success of islet isolation. Many hours may pass from the time the donor is pronounced brain-dead, the time surgical organ procurement begins, and the time the pancreas reaches the islet isolation laboratory. The type of transport solution and quickness of transport are important variables. This situation is in stark contrast to procurement of the pancreas for autoislet transplantation, which has the advantage of only minutes passing between total pancreatectomy in an operating room and transfer of the excised organ to an adjacent islet isolation laboratory. Another difference is the pancreas removed from a deceased donor is likely to be comprised of healthy tissue, whereas the pancreas removed from a patient with chronic pancreatitis is clearly diseased to a highly variable degree. Islet isolation in the laboratory is straightforward for a donated pancreas, whereas this procedure can be extremely difficult and can require varying strategies depending on the condition of the resected pancreas from a patient with chronic pancreatitis.

There are also varying techniques for isolating islets from donor pancreases that favor auto- over allotransplants. Use of collagenase is common to all techniques, and the most common approach, at least for alloislet transplantation, involves use of the Ricordi apparatus for tissue digestion. However, at the final postdigestion step of islet collection, alloislets are usually purified through the use of cold centrifugation during which up to 50% of islets can be lost and the remainder can undergo damage. In contrast, in the autoislet procedure purification of islets is not a primary goal and gentle centrifugation only is usually used for islet separation. The differences in these two approaches stem from the desire to greatly reduce the acinar tissue component in the islet preparation for alloislet transplantation, whereas traditionally in the autoislet scenario this has not been considered necessary and merit is given to the ideas that more gentle treatment of islets will achieve greater yields and the possibility that acinar tissue may contribute to islet neogenesis. One of the primary considerations in purifying islets for both procedures is the emphasis on reducing the mass of tissue to avoid hepatic portal hypertension during infusion of the islets. Portal pressure is monitored during both transplant procedures. A set time limit for infusion is used during which the infusion is stopped temporarily if the portal pressures become excessive. Another major difference in the two procedures is that at the time of transplantation, the alloislet recipient undergoes introduction of a percutaneous trocar to puncture the liver for placement of a catheter that is guided retrograde using imaging to gain entrance into the hepatic portal to establish the infusion site (Fig. 1), which carries the potential complication of intra-abdominal bleeding. In contrast, autoislet infusion is carried out under direct vision while the patient is still in the operating room using a venous tributary that flows into the hepatic portal vein.

ALLO VERSUS AUTO: DIFFERENCES IN NEED FOR USE OF IMMUNOSUPPRESSIVE DRUGS

This is an area where autoislets enjoy a clear advantage over alloislets. Because the chronic pancreatitis patient is the recipient of his own tissue, there is no issue regarding allorejection and no reason for immunosuppression. However, the situation for alloislet transplantation is the direct opposite. Without immunosuppression, islets isolated from an organ donor will undergo hyperacute rejection shortly after transplant. Consequently, a large series of immunosuppressive drugs has been used, searching for agents that will have the fewest side effects for the recipient and the smallest amount of damage to islets. Ironically, many of the drugs that have been used to protect islets from allorejection are toxic to β-cell function (28). During the past two decades, improvements in drug selection and dosage have been able to improve this situation, especially with attempts to eliminate use of steroids and some of the older

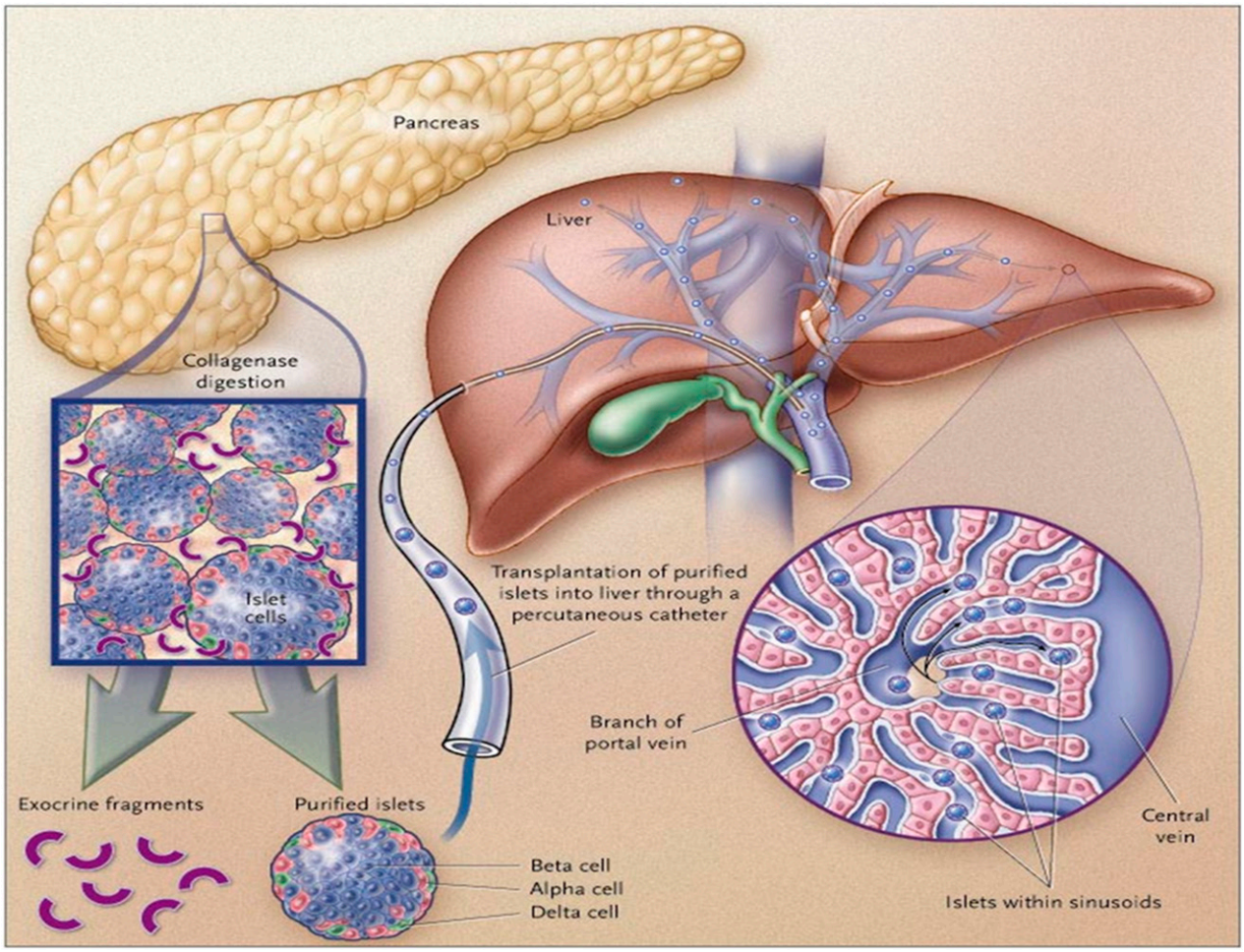

Figure 1—The procedure of alloislet transplantation in T1D recipients. After procurement of a donated pancreas, islets are isolated from the organ through collagenase digestion and purified through centrifugation to separate the islet and acinar tissue. Thereafter, the islets are infused by gravity through a cannula that was introduced percutaneously through the liver and retrograde into the hepatic portal venous system. Portal venous blood flow distributes the islets throughout the liver. Reprinted with permission from Robertson (28).

calcineurin inhibitors. Because the liver is used for transplanting islets, a critical issue stems from the conventional use of systemic venous blood to set goals for blood drug concentrations. The problem is that these goals were created for transplanted organs and not for islet tissue transplanted into the liver where orally administered immunosuppressive drugs are highly concentrated (29,30). Consequently, use of drug concentration goals based on safety decisions related to systemic blood levels when organs such as lungs, liver, kidney, and heart are transplanted do not apply to intrahepatic β-cells. This is especially relevant to combined islet-kidney transplants wherein achievement of the appropriate orally administered drug levels to protect kidneys from allorejection may be deleterious to intrahepatically transplanted β-cells (28–30).

ALLO VERSUS AUTO: DIFFERENCES IN CONSEQUENCES ON POSTTRANSPLANT β- AND α-CELL FUNCTION

After successful intrahepatic islet transplantation, β-cells secrete insulin appropriately during oral and intravenous glucose tolerance tests. A significant correlation between the quantity of islets transplanted and the magnitude of the insulin response to intravenous glucose and intravenous arginine has been established (31). Recently, it has been shown that after correction for the number of islets transplanted, the magnitudes of the acute insulin or C-peptide response to intravenous arginine are comparable with normal subjects who are assumed to have approximately one million islets in their native pancreases (32) (Fig. 2). Strikingly, in the case of autoislets, the linear correlation of the insulin and C-peptide responses and the number of islets transplanted is independent of how many years have passed since transplantation (31,32). This implies that autoislets placed intrahepatically either have very long lives or undergo replication to replace islets that have undergone apoptosis.

There are unique differences in the functionality of α-cells transplanted in the liver compared with islets in the native pancreas. It has been reported that glucagon secretion in response to hypoglycemia after autoislet transplantation in dogs and in humans is defective (33–35). Work in rodents suggests that this absence is due to the intrahepatic site where glycogenolysis and free glucose flux are likely to interfere with α-cell recognition that glucose levels in systemic blood and nonhepatic tissues are in the hypoglycemic range (36). Humans

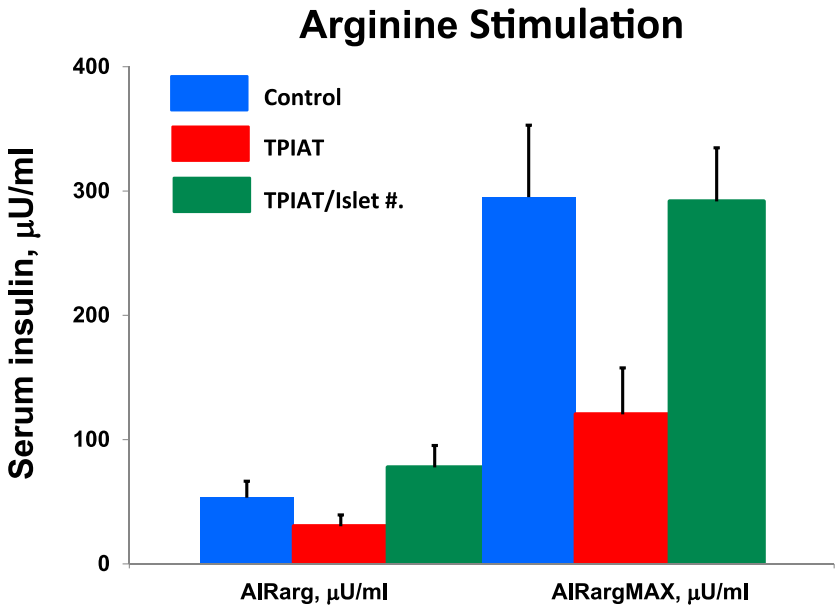

Figure 2—Serum insulin responses to intravenous arginine. AIRarg, the acute insulin response to intravenous arginine over 2–5 min after injection. AIRargMAX, the response to arginine after 60 min of an intervening intravenous glucose infusion, which is known to potentiate AIRarg to a maximum response. Correction of the autoislet recipient responses was performed by dividing their actual AIRarg responses by the number of islets infused in each individual with the assumption that normal control subjects have 1 million islets. There were no differences between control and corrected recipient responses. Adapted with permission from Robertson et al. (32).

receiving alloislet transplants intrahepatically were first reported to have absent glucagon responses to hypoglycemia in 2002 (37), an observation confirmed by Rickels et al. (38) in 2005. Subsequent work has shown a partial glucagon response when glucose levels reach levels <50 mg/dL (39). This study raises the issue of whether this glucagon response might be related to catecholamine release rather than hypoglycemia because epinephrine levels were shown to be elevated 20 min before the glucagon response. Since epinephrine is a known stimulator of glucagon secretion, these results call for similar experiments to be repeated during infusion with adrenergic blockers.

We recently reported a unique examination of this question. This study compared glucagon responses to hypoglycemia in recipients who had received only hepatic autoislets with a group who had received both hepatic and nonhepatic islets (40). Only the group who received nonhepatic islets had a glucagon response to hypoglycemia, and this response was not significantly different from the response observed in normal subjects (Fig. 3). The group receiving only intrahepatic islets had no glucagon response. The hepatic plus nonhepatic site recipients also had normal symptom recognition of hypoglycemia, whereas the recipients of only hepatic site islets had poor symptom recognition of hypoglycemia (Fig. 4). This observation provides functional evidence that use of nonhepatic sites is associated with less recurrent hypoglycemia and thereby preservation of symptom recognition.

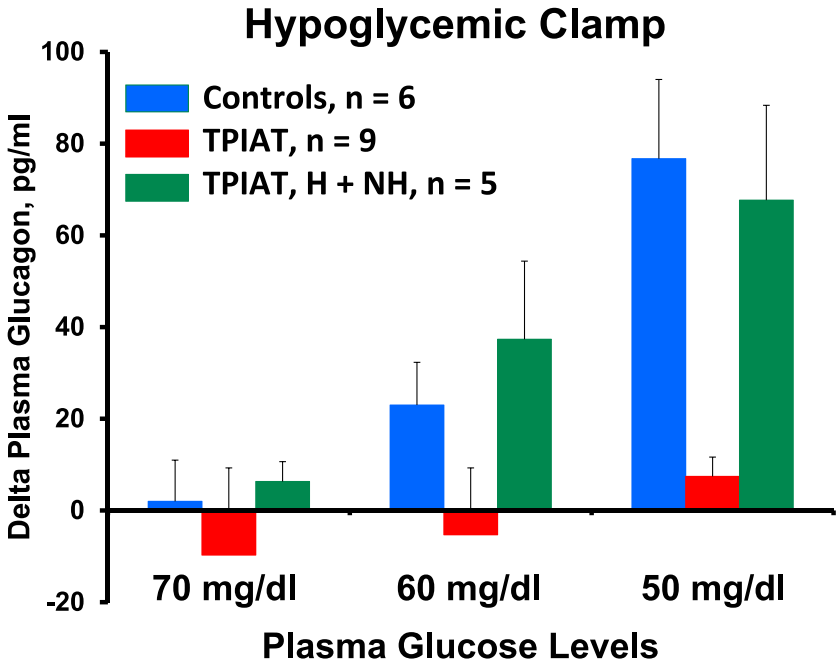

Figure 3—Plasma levels of glucagon during hypoglycemic-hyperinsulinemic clamps. As progressive nadirs were established, normal control subjects had the expected rise in glucagon levels, whereas recipients of autoislets in the liver (H) did not. However, glucagon responses were present in those recipients who had autoislets transplanted in both the liver and a nonhepatic site (H + NH). Adapted with permission from Bellin et al. (40).

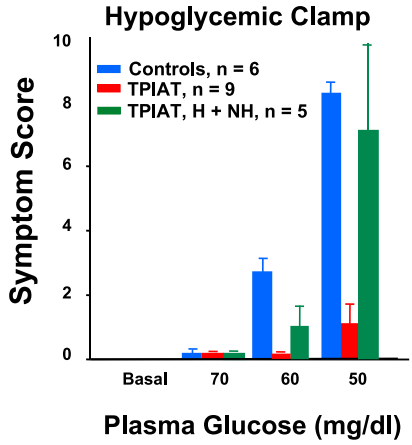

Figure 4—Symptom responses during hypoglycemic-hyperinsulinemic clamps. As progressive nadirs were established, normal control subjects had the expected rise in symptom responses, whereas recipients of autoislets in the liver (H) did not. However, symptom responses were present in those recipients who had autoislets transplanted in both the liver and a nonhepatic site (H+NH). The former group had a history of recurrent hypoglycemia posttransplantation, whereas the latter group did not. Adapted with permission from Bellin et al. (40).

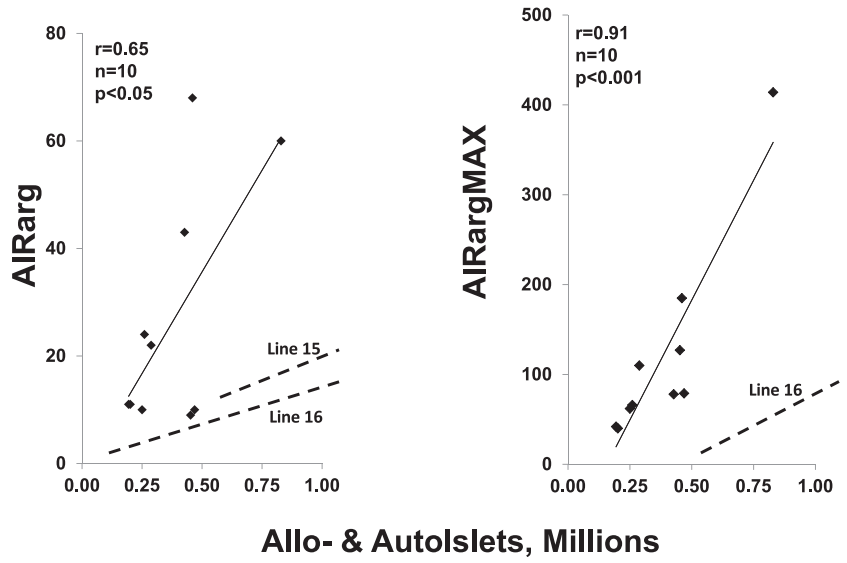

Figure 5—Comparison of the regression lines for AIRarg (the acute insulin response to intravenous arginine over 2–5 min after injection) and AIRargMAX (the response to arginine after 60 min of an intervening intravenous glucose infusion, which is known to potentiate AIRarg to a maximum response) for autoislets and previously published data for alloislets transplanted in T1D recipients. (Line 15: Ryan et al. Successful islet transplantation: continued insulin reserve provides long-term glycemic control. Diabetes 2002;51:2148–2157. Line 16: Rickels et al. β-Cell secretory capacity and demand in recipients of islet, pancreas, and kidney transplants. J Clin Endocrinol Metab 2010;95:1238–1246.) The regression lines for the alloislets were less steep and had smaller slopes than the autoislets. Adapted with permission from Robertson et al. (32).

For this reason, we have recommended that use of the hepatic site for islet transplantation should be accompanied by placement of a significant portion of islets (>100,000) in a nonhepatic site to preserve α-cell responses to hypoglycemia. The reason this is important is that both alloislet and autoislet recipients who return to insulin usage are at risk for hypoglycemia. Although transplantation of alloislets for T1D and autoislets after total pancreatectomy are very different therapeutic propositions, comparison of the results of both procedures can be very instructional. The autoislet procedure, which achieves a much higher rate of success when >300,000 islets are transplanted (Fig. 5), is a very valuable research model for alloislet transplantation and sets the goal for success in terms of islet function and duration of efficacy.

CONCLUSION

The theme of my Perspective is that the future of islet transplantation is very robust. The valuable lessons we have learned in the past 15 years are born of both failure and success. We are steadily making progress in the difficult task of β-cell replacement as a treatment for T1D. Our challenge is to keep doggedly moving the ball downfield as new insights are provided from both the autoislet and the alloislet experiences. A very important point of emphasis is that while the rate of improvement in the results of alloislet transplantation for T1D may be less rapid than we would wish, the more successful procedure of TPIAT is a woefully neglected therapy for patients with chronic, painful pancreatitis. They often needlessly undergo years of poor quality of life that could be obviated by this procedure of proven efficacy.

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