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

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...
that the success rate for islet autotransplantation at 2 years postpancreatec-
tomy 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 post-
transplant success rate of 100% in a
group of seven T1D recipients of allo-
transplantation, 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). How-
ever, 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
insulin independent, 80% were C-peptide
positive but using insulin, and 10% were
C-peptide negative and using insulin. More
recently, reports of alloislet transplanta-
tion have been more encouraging (21–25).

In 2012, Sutherland et al. (26) reported
the rates of success (defined as HbA1c
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 in-
dependence rates of 12, 22, and 72%,
respectively, and partial success of 33,
62, and 24%, respectively. These outcome
are consistent with the autoislet
success rates in another large series re-
ported by Clayton et al. (27). While out-
stripping alloislet success rates, the
autoislet data optimistically point to the
realistic possibility that success rates for
alloislets will similarly increase as im-
provements are made in alloislet procure-
ment, 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 transplan-
tation 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 trans-
plant sites. A great deal of variety exists
in the timing and conditions of the re-
moved 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 procure-
ment 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 con-
trast to procurement of the pancreas for
autoislet transplantation, which has the
advantage of only minutes passing be-
 tween total pancreatectomy in an oper-
ating room and transfer of the excised
organ to an adjacent islet isolation lab-
oratory. Another difference is the pan-
creas 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 pan-
creas, whereas this procedure can be
extremely difficult and can require vary-
ing strategies depending on the condi-
tion 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 transplanta-
tion, involves use of the Ricordi appa-
ratus for tissue digestion. However, at
the final postdigestion step of islet col-
lection, 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 consid-
erations in purifying islets for both pro-
cedures 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 rea-
son for immunosuppression. However,
the situation for alloislet transplanta-
tion is the direct opposite. Without im-
munosuppression, islets isolated from
an organ donor will undergo hyperacute
rejection shortly after transplant.

Consequently, a large series of immuno-
suppressive drugs has been used, search-
 ing 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 allore-
jection are toxic to β-cell function (28).

During the past two decades, improve-
ments in drug selection and dosage have
been able to improve this situation, es-
pecially with attempts to eliminate use
of steroids and some of the older
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 pancreas (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
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.

![Arginine Stimulation](image1)

**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).

![Hypoglycemic Clamp](image2)

**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).

![Hypoglycemic Clamp](image3)

**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).
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 autoislets 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 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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