

## Review article

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# Pancreas transplant in type 1 diabetes mellitus: the emerging role of islet cell transplant

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Pancreas transplant, both whole pancreas and islet cell, is a known therapeutic option for treatment of type 1 diabetes mellitus. Islet cell transplant began as an experimental therapy but is emerging to be quite beneficial due to less surgical risk and fewer complications. It is also considered a promising option in pediatric patients. In this review the authors discuss the indications, procedure, and benefits of islet cell transplant along with newer strategies for improving outcomes.

**Keywords:** Pancreas transplant, Islet cell, Type 1 diabetes, Pediatric diabetes, Hypoglycemia

## Highlights

This article highlights the indications, procedure and outcome of islet transplant. It discusses the pros and cons of the procedure to evaluate how it fares as a treatment modality in type 1 Diabetes in the current era, with a brief insight into its outcome in pediatric patients.

## Introduction

Type 1 diabetes mellitus (T1DM) is an emerging noncommunicable disease, both in India and abroad. It occurs due to the autoimmune destruction of insulin secreting beta cells of the pancreas.<sup>1)</sup> It is associated with both short-term problems of hypoglycemia, hyperglycemia, ketoacidosis, and long-term complications such as nephropathy and retinopathy, among others. The best available medical strategy for achieving normoglycemia is subcutaneous insulin. A basal bolus regimen is currently the most favored approach to keep blood sugar levels in control. Glycemic control is assessed on the basis of glycosylated hemoglobin (HbA1c) levels. Transplant, either whole pancreas or islet cell, is a known therapeutic option for treatment of type 1 diabetes in adults. Initiated as an experimental therapy in the 1980s, pancreatic transplant has been reinvented with timely advances in adult care and is now a commonly performed procedure.<sup>2)</sup>

For a child with T1DM, multiple daily injections of insulin and repeated pricks to check blood sugar as a part of self-monitoring of blood glucose makes life difficult for the patient and the family. The not-so-rigid meal timings of children, their resistance to pricks, parental anxiety, and the risk of hypoglycemia have all indicated the need for a treatment modality that is independent of insulin. Besides, the recommended target HbA1c of <7% is difficult to achieve and the need for stringent blood sugar control poses the risk of hypoglycemia, which is detrimental to the growing brain of the child.<sup>3)</sup> Thus, there is increasing interest in the role of pancreatic and islet transplant in T1DM.

## Categories of transplant (whole pancreas)

Broadly, pancreas transplant consists of three types.<sup>4)</sup>

See the commentary "Islet cell transplantation transitioning to proven therapy for type 1 diabetes" via <https://doi.org/10.6065/apem.2121006edi02>.

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**1. Simultaneous pancreas–kidney transplant**

This is most commonly performed and comprises nearly 70% of cases. It is usually carried out in cases of T1DM with advanced chronic kidney disease due to diabetic nephropathy.

**2. Pancreas after kidney transplant**

This is done in 20% of cases, often after living donor renal transplant or previous simultaneous pancreas-kidney where allograft has failed.

**3. Pancreas transplant alone**

Uncommonly performed, this is done in 10% of type 1 diabetics when renal function is preserved but glycemic control is poor and repeated episodes of hypoglycemia have led to hypoglycemic unawareness. These patients may be struggling with numerous issues leading to noncompliance with insulin therapy.

The results of pancreatic transplant have improved over the years and provide good glycemic control, however, it is an invasive procedure.<sup>5)</sup> Although pancreas transplant is the gold standard, the advent of islet cell transplant has emerged as a promising solution providing insulin independence with normalization of glycated hemoglobin and minimal surgical risk (Table 1).<sup>6)</sup>

Whole pancreas transplant has been a common procedure in adult diabetics but rare in pediatric patients. The probable reasons behind this seem to be that (1) nephropathy and other chronic complications of diabetes are rare in younger patients; (2) intensive insulin therapy is always prioritized by both the clinician and parents over surgical risk; and (3) there were technical hurdles in transplant surgery for the pediatric age group including donor, recipient, and graft rejection issues. Hence, the advent of islet cell transplant appeared to be a promising option as it is not a complex surgical procedure, needs a shorter course of immunosuppression and provides

better glycemic control, although it is still under evaluation for long-term results.

**Islet cell transplant**

**1. History**

From a historical perspective, in 1972 islet cell transplant was first an experiment where islet cell isograft reversed streptozocine-induced diabetes in rats.<sup>7)</sup> In the 1980s, autologous islet cell transplant performed for chronic pancreatitis showed that it was able to maintain long-term normoglycemia. Ricordi et al.<sup>8)</sup> achieved a breakthrough when they demonstrated that the pancreas could be digested using collagenase, and islets could be separated. Over the years, with the development of the Edmonton protocol for islet preparation and posttransplant treatment, including glucocorticoid free immunosuppressive therapy, the procedure evolved to show insulin independence up to 60%–90% in various studies.<sup>6,9-11)</sup>

**2. Indications**

Table 2 shows the common indications of islet transplant.<sup>11,12)</sup>

**3. Donor**

Pancreas donor characteristics associated with successful isolation of islet cells include:

- Age between 20 years and 50 years body mass index >25 kg/m<sup>2</sup> and ≤30 kg/m<sup>2</sup>.<sup>13-15)</sup> HbA1c <6.5% and normal blood glucose levels at the time of organ donation.
- Warm ischemia <30 minutes and cold ischemia <4 hours (in case of deceased cardiac donors)<sup>16-19)</sup>

**4. The procedure**

A pancreas is recovered from a deceased or brain-dead donor

**Table 1. Important comparisons of pancreas and islet transplantation<sup>5,6)</sup>**

Points to differentiate	Pancreas transplantation	Islet transplantation
Type	Whole organ transplant	Islet cell transplant alone
Indication in diabetes	Complications of type 1 diabetes	Used instead of pancreas transplant in some patients
Indication in chronic pancreatitis	No specific indication	As part of total pancreatectomy and autologous islet transplantation
Pediatric indication	No routine indication	Part of total pancreatectomy and autologous islet transplant
Insulin independence rates	70% at 5 yr	25%–50% at 5 yr
Surgical risk	More	Less
Complications	More	Less

**Table 2. Common indications of islet transplant<sup>11,12)</sup>**

1. Type 1 diabetes mellitus of >5 yr duration with negative C-peptide (fasting and or/stimulated)
2. Type 1 diabetes complicated by episodes of severe hypoglycemia associated with hypoglycemia unawareness and poor glycemic control despite compliant intensive insulin therapy
3. Cystic fibrosis related diabetes
4. Diabetes associated with chronic pancreatitis and following pancreatectomy

by meticulous surgery and transported to the islet isolation center in University of Wisconsin in solution for intracellular preservation.<sup>20,21)</sup> The pancreatic duct is cannulated and active collagenase enzyme is delivered to the islet-acinar interface to extract the islet cells.<sup>22)</sup>

The above process was revolutionized by Ricordi's automated method, which used a chamber to free the islets.<sup>23)</sup> After digestion, multiple washings and recombinant steps, this islet extract is maintained in culture for 24–72 hours before release and clinical transplantation. This improves purification, as contaminated exocrine tissue does not survive well in culture.

Although 10%–20% of the islet mass is lost during culture, the final product has a reduced state of inflammation that decreases immune response, both innate and adaptive. The final product should meet the criteria for safety, purity, potency, and identity.<sup>23,24)</sup> The recipient is started with intensive insulin therapy perioperatively to maintain normoglycemia along with induction and maintenance of immunosuppressive therapy. Intraportal transplant of islet cell may be accomplished via a percutaneous transhepatic route or by open surgery with the former being preferred due to low surgical risk. Percutaneous intraportal islet transplantation is done under fluoroscopic or ultrasonographic guidance or a combination of both, such as the Edmonston group.<sup>21)</sup> The final islet product, suspended in 250 mL of transplant media in an infusion bag, is loaded with heparin (70 units/kg recipient weight) and infused under gravity after confirming the position of the catheter tip by portal venogram.<sup>25)</sup>

### Outcomes of islet transplant (Table 3) and its metabolic benefits

The Collaborative Islet Transplant Registry report of 2014 has shown notably improved outcomes, both short- and long-term, with achievement of insulin independence in up to 80% of patients with favorable factors such as autoantibody negative for islet antigen, islet mass >5,000 islet equivalents (IEQ)/kg, among others.<sup>23,26,27)</sup> The minimal beta cell mass for a significant effect after transplant is greater than 5,000 IEQ per kg of the recipient body weight.<sup>28)</sup> Some centers claim to have insulin independence rates of 50%–70% by five years after the transplantation approaching those of patients of type 1 diabetes with whole pancreas transplant.<sup>29-31)</sup>

Studies have revealed that endogenous insulin secretion from transplanted islets led to near normalization of blood glucose. It also resulted in decreased basal hepatic glucose output and normal plasma amino acid levels. Transplant restores glucagon secretion, normalization of hepatic glucose production, and improvement in lipid profile and insulin mediated protein kinetics. Clinical benefits seen are numerous and significant (Table 4). Well controlled HbA1c levels were seen after transplant in patients off insulin, although insulin independence seemed to decrease over a period of time. Even with intensive blood glucose monitoring, no other insulin regimen can achieve such goals.<sup>32)</sup> The success of pancreas and islet transplant in treating severe hypoglycemia led to its being recommended as a therapeutic option in cases of problematic hypoglycemia.<sup>33)</sup>

**Table 3. Outcome of islet transplant**

Study	Subjects	Insulin dependence at 1 year	Year
Ryan et al. <sup>40)</sup>	Adult (n=65)	68%	2005
Trial by Immune Tolerance Network <sup>28)</sup>	Adult (n=36)	44%	2006
Bellin et al. <sup>34)</sup>	Pediatric (n=24)	78%	2008
Japanese Trial of Islet Transplantation <sup>41)</sup>	Adult (n=18)	17%	2009
Sutherland et al. <sup>12)</sup>	Adult and Pediatric (n=409)	30% at 3 yr (25% in adults, 55% in children)	2012
Chinnakotla et al. <sup>35)</sup>	Pediatric (n=75)	41.3% (31 of 75) achieved insulin independence. 28 of 31 patients achieved insulin independence within 1 year.	2014
Johnston et al. <sup>42)</sup>	Adult (n=36)	33.3%	2015
Hering et al. <sup>43)</sup>	Adult (n=48)	52.1%	2016
CITR annual report <sup>44)</sup>	Adult and pediatric (n=877)	50%	2015
Bellin et al. <sup>45)</sup>	Pediatric (n=17)	82%	2017
Kirstie et al. <sup>46)</sup>	Adult	60%	2020

CITR, Collaborative Islet Transplant Registry.

**Table 4. Pros and cons of islet cell transplant<sup>11,14,32,33,39)</sup>**

Pros	Cons
Improved quality of life	Low donor availability
Prevention of recurrent diabetic nephropathy	Process of islet isolation and purification is tedious with low yield
Freedom of exogenous insulin with normal glucose	Risks associated with immunosuppression
Marked reduction in episodes of hypoglycemia	Procedure requires expertise
Normalization of glycosylated hemoglobin	Risk of routine operative risk
Less stringent dietary restrictions	Expensive
Less frequent blood glucose monitoring	Less long-term data on safety and outcome
Stabilization of or reduced secondary complications	Still not the standard recommended procedure for treatment of type 1 diabetes mellitus

Reduced frequency of blood glucose monitoring and freedom from insulin injection is a huge benefit in the pediatric population, as frequent pricks can be frightening for them.

### Pediatric outcomes

Pancreas and islet transplant is uncommon in children with diabetes due to the reasons enumerated above. Hence the experience in pediatrics is limited. Islet cell transplant was tried and considered better than whole pancreas transplant, which poses major operative risks. Other disadvantages of the latter include chronic immunosuppression and its related side effects and posttransplant complications. Islet transplant in the pediatric age group has been conducted mostly for chronic pancreatitis after total pancreatectomy where improvement in pain resolution and quality-of-life were comparable to adults, with >80% of recipients being able to attend school or work.<sup>34)</sup> Rates of insulin independence were seen up to 40% at two years post islet transplant in these children. More than 50% of the youngest recipients between five and 12 years of age were insulin-independent at 1 year post islet transplant. During three years of follow-up in pediatric patients, HbA1c <7.0% was maintained in 100% who received >5,000 IE/kg.<sup>11,35)</sup> So younger age and shorter duration of pancreatitis have been associated with higher islet yields, as in adults.<sup>36)</sup>

Avoiding a major operative procedure and opting for a less invasive islet cell transfer therapy is quite alluring but it needs to be poised against the scarcity of donors and difficulties faced in processing the islet cells. Besides, there is a lack of equipment and expertise in successful performance of such complex procedures. In pediatric ages, especially when development of complications due to diabetes is not imminent in the near future, the balance between the efficacy and toxicity of the procedure needs to be evaluated. As there is little experience of islet cell transplant in the pediatric age group, long-term studies are needed to evaluate the outcome of transplant in cases in chronic pancreatitis in children. Even more experience is needed for such procedures in children with T1DM, and their outcome on follow-up needs to be studied. Only then can better insight be available about the future of such a procedure in the pediatric age group.

### Technological advances

Newer developments in transplant procedures have made it possible, to some extent, to overcome existing barriers such as scarcity of donors and immune reactions leading to rejection. Porcine islet cells have been used to form xenoislets for transplantation, but immune rejection was a drawback. Extensive studies are being carried out to investigate the ability of human embryonic stem cells and induced pluripotent stem cells to differentiate into functional insulin producing cells. This may lead to successful use of such cells for transplant.<sup>37)</sup>

To protect against immune reactions, islet encapsulation is another advanced method of islet transplantation. Isolated

islets of human origin or porcine xenoislets are encapsulated in a semipermeable membrane that allows the passage of nutrients and hormones but prevents cell contact with immune cells and hence, protects against immune reactions. This can be particularly beneficial for xenotransplantation.<sup>38)</sup> When multiple islets are encapsulated within a device >1 mm in diameter, it is called macroencapsulation. It is usually placed in an extravascular space. Microencapsulation means coating of islets in an immunoprotective cover.

Several innovative drugs are being tried to limit reduction of transplanted islet cell mass in the posttransplant period. Efforts are being made to improve the efficacy of islet graft with the minimal toxicity of immunosuppressive therapy. Several methods to reverse diabetes with cellular replacement of insulin secreting cells, along with ways to prevent recurrent autoimmune destruction of the newly transplanted cells, are under study.

### Conclusion

Diabetes mellitus is a chronic debilitating disease associated with macrovascular and microvascular complications. Maintaining euglycemia is crucial to preventing complications and also reversing their progression. Currently, intensive insulin regimes have contributed to maintenance of normal blood glucose levels, which is an uphill task, and more so in the pediatric population. Emergence of islet transplant as an experimental procedure and its evolution over the last 2 to 3 decades has opened new avenues in the treatment of T1DM. A great deal of research and experiments in islet transplant are evolving to provide a novel strategy for providing successful normalization of HbA1c with insulin independence. Its lower surgical risk, and the reduced toxicity of immune therapy with lower risk of complications makes it an ideal future prospect of treatment in the pediatric age group. The major limiting factor in transplant success is the wide gorge between demand and supply due to organ shortage, however, new avenues of research have led to numerous developments that seem to overcome the existing barriers. Still, multicentric trials on follow-up of the transplant procedure are needed before recommending it as a routine therapeutic option for T1DM.

### Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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