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Islet Transplantation in Children

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Abstract
Purpose of Review Transplantation of the islets of Langerhans or the pancreas aims to restore blood sugar control. We review both forms of transplantation in children.
Recent Findings Allogenic islet transplantation typically in to the liver via the portal vein may be a potential alternative to pancreas transplantation in the future. Autologous islet transplantation after total pancreatectomy is effective for debilitating symptoms of recurrent and chronic pancreatitis. Chronic pancreatitis in children is most often related to genetic mutations but is otherwise similar to adults with eventual exocrine and endocrine failure. Removal of the pancreas ameliorates pain, and islet transplantation preserves endocrine function to the extent allowed by the damage sustained by the pancreas from chronic inflammation.
Summary Despite the complexity of the operative procedure, the outcome of total pancreatectomy and autologous islet transplantation in children has been excellent including quality of life.

Keywords Pancreatectomy · Autologous · Allogenic

Introduction

Pancreatic islets (of Langerhans) comprise a miniscule volume of the pancreas yet are the primary control for blood sugar and therefore central to the worldwide problem that is diabetes mellitus (DM). Despite this vital role, the pancreas is not a necessary organ. Indeed, both the endocrine and exocrine functions of the pancreas can be replaced by injectable insulin and oral pancreatic enzyme supplements, respectively. It is however apparent that while exogenous insulin is adequate for treatment of pancreatic islet loss, the precise control that is necessary to prevent long-term complications of diabetes remains a problem. Apart from beta cells for insulin production, islets also produce other hormones, most notably glucagon, a counterregulatory hormone to insulin. The control of blood sugar is therefore not simply a matter of releasing more or less insulin. In culture small islets will migrate and coalesce to form larger islets, implying that there is an advantage to the cells of the islet being in close proximity. While the two parts of the pancreas are dichotomous in function, it is not uncommon for individuals with DM to develop exocrine pancreatic dysfunction, indicating that insulin has a regulatory function on the exocrine portion of the gland [1]. The endocrine part of the pancreas can function quite adequately in the absence of the exocrine part of the gland. This is most clearly demonstrated in cystic fibrosis (CF) patients; in the classical form of this disorder, exocrine dysfunction is present from birth while endocrine function is normal.

Pancreatic Disease in Childhood

As with many autoimmune disorders type 1 diabetes mellitus (T1DM) often presents in childhood and represents the most prevalent disease of endocrine origin in childhood. While type 2 diabetes mellitus (T2DM) has been traditionally thought of as a disorder of adults exclusively with increase in obesity and related metabolic syndrome in younger individuals, this is no longer the case. The most prevalent disease to affect the pancreas resulting in exocrine pancreatic failure is CF. Exocrine pancreatic failure is a pathognomonic feature of CF that

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results directly from the primary disorder affecting the secretory elements of the pancreatic ductal system [2]. Diabetes related to CF correlates with development of progressive liver disease in CF and may be explained by the shared ontogeny of the ductal systems of the pancreas and biliary tree. It follows that involvement of the hepatic parenchyma and pancreatic islet system are both secondary progression of the disease.

Primary pancreatic disease of the exocrine portion can be otherwise divided in to pancreatic exocrine failure and inflammation in the form of acute, recurrent, and chronic pancreatitis (CP). Outside of CF primary exocrine failure is uncommon in children, though there is a list of well-known syndromes that comprise exocrine dysfunction as part of the overall syndrome [3]. Massive damage such as direct trauma or repeated damage of the exocrine pancreas as in recurrent and chronic pancreatitis will eventually lead to exocrine and potentially endocrine dysfunction [4]. Diseases common in adults such as alcoholic pancreatitis and gallstone–related pancreatic ductal obstruction are not seen in pediatric practice, though the latter may be more of a problem with increasing prevalence of cholelithiasis among young obese individuals. Drug-related acute chemical pancreatitis is well known in hospitalized patients in general. Chronic pancreatitis in children and young adults is an unusual occurrence. As reported by Schwarzenberg et al., 67% of cases of CP are related to a genetic mutation [5•]. The other one third is related to possible structural disorders of the pancreas. Pancreas divisum is typically mentioned in this regard and likely represents a risk factor for CP, although it is a common finding in the general population. Among genetic disorders most commonly CP in childhood is due to a mutation in the cationic trypsinogen gene (PRSS1), the serine protease inhibitor Kazal type 1 (SPINK1), or the CF transmembrane conductance regulator (CFTR) [6]. We have previously reported that pancreatic disorders characterized by cysts are otherwise rare [7].

Pancreas Transplantation Versus Islet Transplantation (Table 1)

Unlike the need for regular dialysis for renal failure, the prospect of taking pancreatic enzymes for exocrine failure and insulin for T1DM are much more easily manageable. So the question arises as to whether and under what circumstance a pancreas transplant is even necessary. And by extension whether transplantation should include the whole organ or is there an advantage to transplanting the islets only. It can be agreed that there is no indication for transplanting the pancreas for the exocrine function of the gland. Apart from pancreatic enzyme supplementation, food itself can be made elemental to aid absorption.

In general, abdominal organ transplantation began in the 1960s and has been a remarkable success. Pancreas transplant was first performed by Kelly and Lillehei at the University of Minnesota in 1966 and is a standardized therapy at this time [8]. Interestingly, around the same time, the idea of islet cell isolating was also in development [9]. Currently, pancreas transplants are performed in relation to kidney transplant or as an isolated pancreas transplant to mitigate life-threatening complications related to T1DM. This has evolved to the point that 90% of pancreas transplants are performed simultaneously with kidney transplantation (SPK) according to the most recent United Network of Organ Sharing (UNOS) data for the USA [10]. A much smaller number of pancreas transplants are performed as compared to cadaveric liver and kidney transplants. For instance, the UNOS data for 2016 shows approximately 13,500 cadaveric kidney transplants versus < 1000 pancreas transplants in adult patients [10, 11]. Living donor transplantation is routine for kidney failure with the above UNOS data showing that > 5000 living donor kidney transplants performed in the same year. There is no equivalent to kidney dialysis for liver failure, and therefore, liver transplantation is a life-saving procedure. Liver wait-list deaths lead to some remarkable advances in surgery now around three decades ago that include living donor liver transplantation using either a part or the whole of the left lobe or the right lobe of the liver and splitting a cadaveric liver [12–14]. Although conceptually possible, living donor partial pancreas transplantation has not so far been pursued as a clinical option. In comparison to the kidney and liver, the wait-list for pancreas transplantation has been on the decline over the past several years per UNOS records though may have stabilized per the most recent statistics [10]. Similarly worldwide, the data indicates that there has been a steady drop in the numbers of transplants.

Table 1 Important comparisons of pancreas and islet transplantation

	Pancreas transplantation	Islet transplantation
Indication; diabetes	Complications of type 1 diabetes	Experimental treatment
Indication: pancreatic disease	No specific indication	Chronic pancreatitis; as part of total pancreatectomy and autologous islet transplantation
Pediatric	No routine indication	Part of total pancreatectomy and autologous islet transplant
Future prospects	Less commonly performed in view of competing therapies	More commonly performed in association total pancreatectomy

While there are many ways to debate as to why this has occurred, the prospect of improved therapies for T1DM is proposed to be an important reason.

Pancreas Transplantation in Children

It follows from the argument above that there should rarely be an indication for an isolated pancreas transplant in children, and this is indeed the case. Specifically, because long-term complications of T1DM are not seen in childhood, the only true life-threatening indication for pancreas transplantation in children is therefore hypoglycemia [15]. Somewhat ironically, pancreas transplants are performed in a group of children with normal pancreata. This is the case for children with intestinal failure and liver disease who require a liver and small bowel graft. Historically, this particular situation has occurred most commonly in small children with very short bowel secondary to resection related to gastroschesis, mid-gut volvulus, and necrotizing enterocolitis in the main [16]. These infants have been most susceptible to end-stage cholestatic liver disease during the first year of life and require a liver in addition to a small bowel graft. Rather than piecemeal two separate grafts for the liver and small bowel, Thomas Starzl and others developed a technique of harvesting the hepatobiliary, pancreas, and small bowel components as a single matrix and transplanting them en bloc so that multiple anastomoses are not required in the recipient [16]. Overall, bowel transplant including multiple organs has been successful as shown by recent data from our center [17]. Of course, the recipient of a liver bowel graft is left with owning two pancreata. In practice, this does not appear to cause any problem with over exuberant blood sugar control. As regards exocrine function, despite this configuration, we have noted pancreatic insufficiency for the first few months after transplantation in some patients [18].

The published literature on pancreatic transplantation in children outside of the liver bowel transplant group is limited. There are few data scattered over time, and it is uncertain as to what the data would look like now if pancreas transplant had been more routine in past decades in children [19••]. In general, transplantation has been considered, where the pancreas graft can be additional to a more necessary transplant. One such situation as noted above is liver and endocrine pancreatic failure developing in individuals with CF. For instance, Mekeel et al. from the University of Florida reported nine children with CF who underwent liver transplantation; three of nine received an en bloc liver pancreas transplant for insulin-dependent diabetes [20]. It was noteworthy that diabetes developed in some individuals after isolated liver transplantation. Not surprisingly, less oral pancreatic enzyme supplementation was necessary after transplantation in those with a pancreas graft. Other centers have also reported similar cases of en bloc transplants in children with CF and other rarer disorders as published by our group [21, 22]. In a survey of transplant centers by Bandsma et al., over 60% indicated that they would perform a simultaneous liver–pancreas transplant in the setting of CF-related liver disease and diabetes [23••]. Interestingly, only eight actual such transplants emerged to have been performed from over 80 centers in older children and young adults. As would be expected, the eight patients required insulin pretransplant. One of the eight developed a recurrence of insulin requirement on long-term follow-up. Also concerning was that half the individuals developed major posttransplant complications. Even with these small data, certain questions arise. Firstly, even in the presence of a liver graft, 1/8 pancreas grafts failed. This may not be reasonable; we have previously shown that in individuals with CF undergoing lung transplantation, a combined liver graft improves the long-term outcome [24]. Similarly, other organs appear to be given some "protection" from the addition of a liver graft. In the absence of a greater pool of data, the question will go unanswered as to whether there should be more routine consideration of a pancreas graft to be combined with the liver graft in patients with CF.

Islet Transplantation—Autologous

Islet cell transplantation can be broadly divided in to two groups: "autologous," also known as "autotransplantation," and allogenic." Autologous islet transplantation after pancreatectomy (TPAIT) involves removal of the pancreas followed by liberation of the islets from the pancreas and reimplantation of the islets in a suitable site [25]. From a surgical standpoint, the c-loop of the duodenum is removed along with the pancreas and most often the spleen. The remaining duodenum is reconstructed after the pancreatectomy and a hepaticojejunostomy created for biliary drainage. At our center, abdominal closure is delayed typically 3–4 h during which time the pancreas is taken to a dedicated islet isolation laboratory (Fig. 1) and islets extracted. A detailed account of our islet isolation process has been previously published [26, 27]. As is the case with most centers, we consider the liver to be the most suitable host for the islets and the islets are injected in to the portal vein using a standard intravenous catheter while monitoring portal vein pressure throughout the infusion (Fig. 2). One major difference to the procedure favored by some centers involves immediate closure of the abdomen after intestinal reconstruction and percutaneous approach to accessing the portal vein for islet infusion by interventional radiology. Intrabdominal sites other than the liver that have been found to be effective to host islets include inside the capsule of the kidney, omentum, and abdominal cavity. Other variations to the surgical procedure in terms of the configuration of the jeunum and gastric drainage have also been published [15]. We have previously demonstrated how

Fig. 1 Dedicated islet cell laboratory

preservation of the vascular supply of the pancreas as long as possible through a prolonged operative procedure to remove a chronically inflamed pancreas helps to reduce ischemic time and preserve more islets for eventual reimplantation [28].

The main indications for TPAIT are recurrent and CP. Acute pancreatitis as an isolated occurrence is not uncommon; however, recurrent and CP are relatively rare. With frequent recurring pancreatitis or CP patients are plagued with pain that they cannot manage to the point that some will consider suicide. With pain comes increasing pain medication use, specifically narcotics, and the individual may be labeled as being addicted to narcotics. Needless to say, the individual becomes severely debilitated, impacting work and home life. Apart from loss of exocrine and eventual endocrine function, CP spanning decades is a risk for pancreatic cancer as indicated by the current thinking around pathophysiology of pancreatic cancer, chronic pancreatitis, and the "two-hit theory" [29]. Therefore, we believe that there are multiple reasons to consider TPAIT once CP has been diagnosed. Other options are limited, and certainly, there is no specific medical treatment other than to treat the pain; endoscopic and surgical options could be considered in individuals with pancreatic ductal obstructive problems. While TPAIT surgery is extensive, it is the only way to alleviate the pain after failure of these other attempts at treatment. It goes without saying that the best results from salvaging the islets comes from patients with the least disease or destruction of the pancreas and that individuals with long-standing disease spanning many years are likely to have a greater loss of islets from the disease. Furthermore, liberating islets from a hard, calcified pancreas will reduce the likelihood of recovering adequate islets for the patient not to need insulin after TPAIT. The largest experience with TPAIT is from the University of Minnesota [30]; almost 60% of adults were shown to be pain free at 2 years while two thirds of children were pain free on follow-up. Only 25% of adults and 55% of children were insulin independent on follow-up.

Islet Transplantation—Allogenic

Allogenic transplantation of islets is essentially pancreas transplantation without the exocrine portion of the gland, and therefore, the primary indication for this therapy is T1DM. As noted above, pancreas transplantation is largely performed as SPK transplants. It follows that benefit of pancreas transplant is considered as secondary and not mandatory as compared to kidney transplant. The circumstances under which one would consider islet transplantation over pancreas transplant are unclear. Technically, islet transplant makes sense in a number of ways when compared to pancreas transplantation. Specifically, islet transplantation employing interventional radiology for portal venous infusion of islets is much less invasive than abdominal surgery. Despite advances in islet isolation, donor selection, and immunosuppression, it remains unclear as to whether long-term insulin independence is possible with current developments [31].

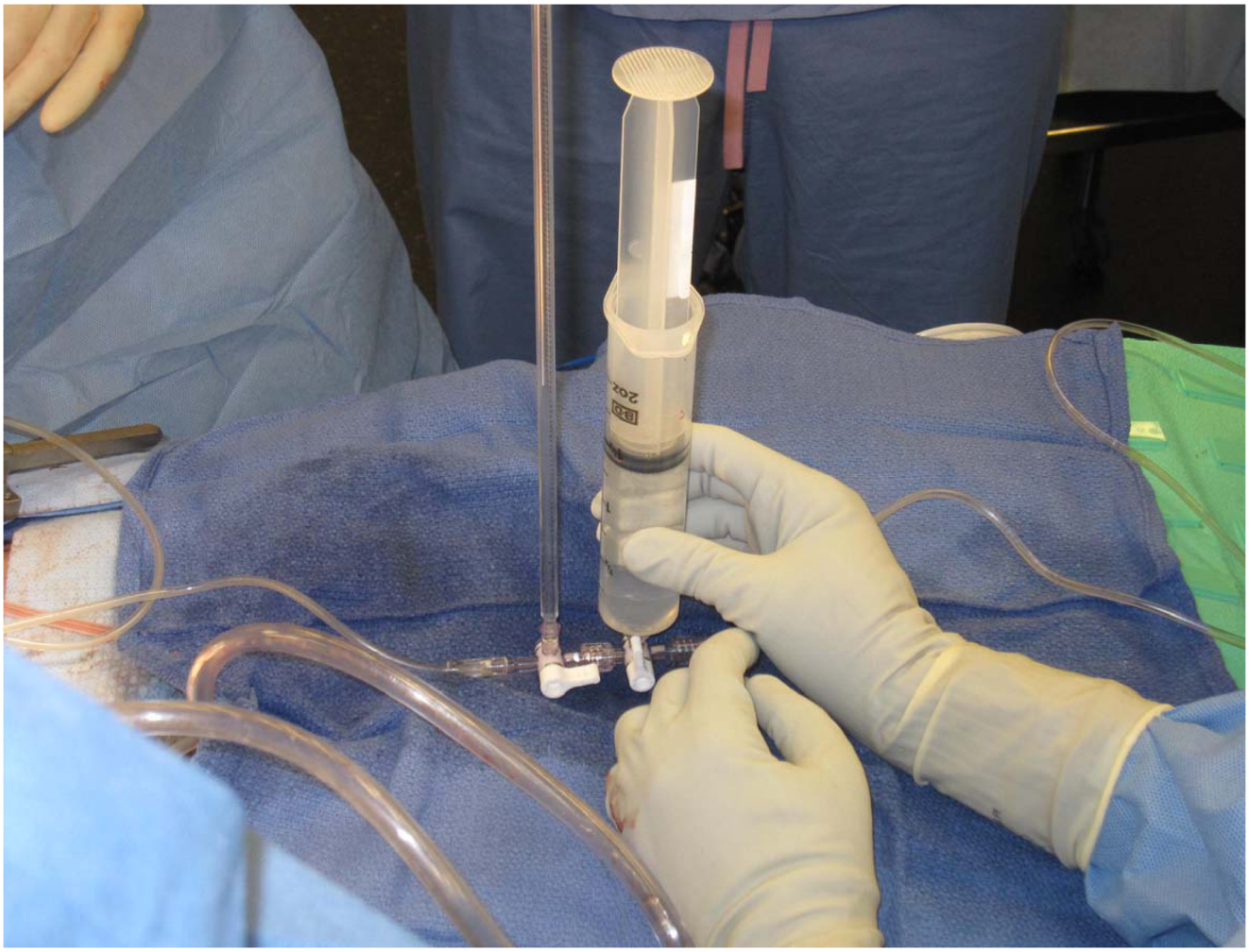

Fig. 2 Intraoperative portal pressure monitoring

Islet Transplantation in Children

The most appropriate indication for TPAIT is the specific group of children with inherited causes for recurrent and CP. These children can be symptomatic from early in life or symptoms may appear throughout childhood or indeed as adults. Occasionally, the pancreas can be atrophic without much symptomatology so that the child will present with exocrine pancreatic failure. In an extensive survey of the French population by Rebours et al. of individuals with hereditary pancreatitis, two thirds of who were positive for the PRSS 1 mutation, there was absolute and relative increase for pancreatic cancer [32]. A timely intervention in the form of TPAIT has clear benefits for this group; it has been noted that islet yield is greater in children as compared to adults [33]. Furthermore, the islet yield is greatest in the youngest children [34]. The response to surgery in terms of symptomatology is also better than in adults [35]. Recurrent or CP outside of genetic disorders is very unusual and likely needs to be considered on an individual basis. It can be expected that some will have issues related to pancreatic duct obstruction and may be amenable to surgery [5•]. There should be greater scrutiny for an anatomical defect in these individuals.

Allogenic islet transplantation for T1DM has not been pursued to any extent clinically in children. Given the data from adults, it is difficult to imagine the success rate in children. It can be envisioned that as islet graft survival improves and islet transplantation is performed more routinely in adults, there will be a gradual increase in the number of children undergoing the procedure. There are however some differences in children especially if we are looking for islet function to last a life time. Using liver transplantation as an analogy, we would expect that for a pediatric patient, the ideal graft would be from a pediatric or young adult donor for the best long-term outcome. Unlike the liver, cadaveric pancreata from very young children make poor grafts for isolated islet transplantation and currently pancreata from young children are only used as part of multivisceral grafts. The remaining group of available cadaveric pancreata is from elderly donors not suitable for pancreas transplantation; the long-term outcome of

islets from these pancreata is unclear. With ongoing developments in islet transplantation, the situation may improve. In particular, improvements in immunology and developments in culture, preservation and ultimately the potential to clone and or grow islets may be the answer. At the same time, it can also be argued that developments in insulin and its administration as well as technological improvements are already leading us to an artificial endocrine pancreas that can adequately mimic islet function.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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