Autologous Islet Cell Transplant

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Abstract

Transplantation of islets isolated from autologous pancreas, commonly called *islet autotransplantation* (IAT), has been developed primarily for the treatment of refractory chronic pancreatitis (CP). CP is an irreversible and progressive inflammatory disease of the pancreas in which the patients often experience severe abdominal pain and malnutrition. Diabetes can result in advanced stage CP if the inflammatory response damages pancreatic islets. Multiple causes such as genetic mutations, alcohol abuse, autoimmunity, recurrent acute pancreatitis, and obstruction of the pancreatic duct are involved in the development of CP. Medication and endoscopic procedure are available for CP treatment; however, a significant portion of CP patients are eventually referred to a surgical clinic. Surgical resection of the inflamed pancreas is a treatment option if CP patients do not respond to other means of treatment although there is loss of pancreatic exocrine and endocrine functions after even a partial resection of an inflamed pancreas. IAT following total pancreatectomy (TPIAT) allows elimination of severe abdominal pain while preserving pancreatic endocrine function in a single operation. TPIAT has been applied for the treatment of benign pancreatic tumors in addition to CP. Due to the remarkable improvements in islet isolation methodologies and surgical procedures, there is a significant increase in the number of transplants and improved graft outcomes. Future directions of TPIAT include changes to current patient selection criteria and enhancing islet graft function by inhibition of the peritransplant inflammatory reaction.

Keywords

Chronic pancreatitis · Pancreatic islet isolation · Islet infusion · Inflammatory response

Introduction

Chronic pancreatitis (CP) is an irreversible inflammatory disease that develops pancreatic exocrine insufficiency and, later on, leads to the failure of the endocrine tissue in the Islets of Langerhans (Braganza et al. 2011; Etemad and Whitcomb 2001). The total number of hospitalizations due to CP in the USA has been reported to be more than 56,000 annually, which resulted in a sum of over $600 million per year for medical costs (Everhart and Ruhl 2009). Surgical procedures are considered when medication and/or endoscopic therapy have failed. Total pancreatectomy (TP) for severe CP was first successfully performed in November, 1944. However, the patient was found dead in her home due to severe hypoglycemia ten weeks after TP (Waugh et al. 1946; Whipple 1946). As such, a major risk of pancreatic removal is surgical diabetes, which causes severe hypo- and hyperglycemia (Matsumoto 2011). David Sutherland first performed TPIAT at the University of Minnesota in 1977 to reduce the risk of surgical diabetes and to eliminate severe abdominal pain (Najarian et al. 1979). A total of 525 recipients of autologous islets have been registered in the Collaborative Islet Transplant Registry (CITR), the international registry for pancreatic islet transplantation (Coordinating Center 2014). At present, the largest series of TPIAT in the world has been reported from the University of Minnesota (over 450 recipients) (Sutherland et al. 2012). Other major US centers performing TPIAT include the University of Cincinnati, Medical University of South Carolina, the University of Alabama, and the Cleveland Clinic. Baylor University Medical Center has performed more than 100 cases since it initiated a TPIAT program in 2006.

Etiology of Chronic Pancreatitis

Chronic pancreatitis (CP) is defined as a progressive inflammatory disease caused by one or multiple factors (Conwell et al. 2014; Etemad and Whitcomb 2001). Well-known risk factors of CP include heavy alcohol consumption and smoking (Muniraj et al. 2014). The M-ANNHEIM classification, a clinical classification system of CP, identifies alcohol consumption, nicotine consumption, nutritional factors of high fat and protein, hereditary factors, efferent duct factors, autoimmunity, and rare metabolic diseases as risk factors (Schneider et al. 2007). According to the North American Pancreatitis Study 2 (NAPS2), a multicenter trial for CP procedures conducted between 2000 and 2006 where 539 patients were enrolled, 44.5% of the CP cases were determined to be alcoholic CP (Cote et al. 2011). The alcoholic CP cohort of the NSAP2 study consisted of 28.6% of idiopathic, 8.7% of genetic, 2.2% of autoimmune, 8.7% of obstructive, and 7.2% of the other causes (Cote et al. 2011). This proportion of alcoholic CP, however, was less than previous reports and the authors' estimation. A clinical study at Mayo Clinic from 1976 to 1982 reported that the proportions with any alcohol consumption and heavy alcohol consumption in CP patients were 84% and 58%, respectively (Layer et al. 1994). Smoking is also considered an independent risk factor of CP. Smokers were 7.8–17.3 times as likely as nonsmokers to develop CP, and this ratio was directly proportional to the amount of smoking (Lin et al. 2000; Talamini et al. 1999). Another major risk factor of CP is abnormal findings in the pancreatic duct: pancreas divisum, annular pancreas, pancreatic duct stenosis/obstruction, and sphincter of Oddi dysfunction. According to the classical understanding of CP development, excessive pancreatic enzyme activity, autolysis, and repeated inflammation are involved in the development of CP although the detailed mechanism of CP is still unknown (Witt et al. 2007). The symptoms of CP such as malnutrition and diabetes are seen in the advanced phase of the disease.

Regarding hereditary pancreatitis, Whitcomb and colleague identified a mutation in the cationic trypsinogen gene (Protease, serine, 1; PRSS1) as a cause of hereditary pancreatitis in 1996 (Whitcomb et al. 1996). Subsequently, other mutations of PRSS1 and mutations in SPINK1, CTRC, CFTR, and CPA1 have been reported to be associated with CP development (Cohn et al. 1998; Sharer et al. 1998; Witt et al. 2013; Witt et al. 2000; Witt et al. 2006). More recently, hereditary chronic pancreatitis has been considered as a disease caused by complex multiple gene mutations that regulate pancreatic enzyme activity (Masamune 2014). PRSS1 and SPINK1 have been demonstrated to increase trypsin activity. PRSS1 is a cationic trypsinogen gene. Mutation variants including p.R122H and p.N291 in PRSS1 are associated with CP onset (Masamune 2014; Whitcomb et al. 1996). SPINK1 is pancreatic secretary inhibitor, and Witt et al. reported that 22 out of 96 juvenile CP patients had PRSS1 mutations including p.N34S and c.194+2 T>C (Witt et al. 2000). Chymotrypsin C (CTRC) degrades all human trypsin trypsinogen isoforms with high specificity (Rosendahl et al. 2008; Szmola and Sahin-Toth 2007). The loss of CTRC activity, therefore, would impair the protective trypsinogen- and trypsin-degrading activity of CTRC (Zhou and Sahin-Toth 2011). Rosendahl et al. found two alterations (p.R254W and p.K247_R254del) that were significantly overrepresented in pancreatitis patients (Rosendahl et al. 2008). Regarding CPA1 (carboxypeptidase A1), Witt et al. showed that functionally defective CPA1 variants are associated with pancreatitis, especially early onset pancreatitis (Witt et al. 2013).

Autoimmune pancreatitis (AIP) is classified histologically as type 1 and type 2 according to the International Consensus Diagnostic Criteria (ICDC) presented in 2011 (Kawa et al. 2014; Shimosegawa et al. 2011). Histologically, type 1 AIP is characterized by lymphoplasmacytic sclerosing pancreatitis (LPSP). Type 2 AIP is characterized by idiopathic duct-centric pancreatitis (IDCP) with granulocytic epithelial lesions (GEL). Type 1 AIP is now considered as a

component of multisystemic IgG4 disease. A cohort study in the UK showed that serum IgG4 was elevated (>1.4 ng/l) by up to 70% above normal at diagnosis and up to 77% above normal during follow-up (Huggett et al. 2014).

Pancreatic divisum and sphincter of Oddi disorders are risk factors that can induce congestion of pancreatic enzymes and increase pancreatic exocrine enzyme activity due to mixing of fluids from the bile duct into pancreas (Tarnasky et al. 1997). After differential diagnosis, these patients will be classified etiologically using the TIGAR-O criteria, which also suggest potential treatment options (Etemad and Whitcomb 2001; Huggett et al. 2014).

Diagnosis of CP

CP can be diagnosed by present clinical symptoms, medical history, family history, laboratory data, and image analysis such as transabdominal ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI), although no CP-specific reliable biomarker has been established. CP patients commonly show severe abdominal pain (such as upper abdominal pain) or back pain, which may be exacerbated by intake of a high-fat diet or alcohol. Patients often lose their appetite and body weight can drop, leading to malnutrition because of nausea, vomiting, and/or diarrhea. In the laboratory data, the activity of pancreatic enzymes such as amylase or elastase increases with the onset of symptoms and correlates with an increase in the number of white blood cells (WBC) and a higher level of C-reactive protein (CRP).

The transabdominal US, CT, and MRI are noninvasive clinical imaging procedures to confirm CP. However, these studies are not sensitive enough to diagnose the early stages of CP (Rosendahl et al. 2007). The pancreas with advanced stage CP demonstrates morphological changes including atrophy, calcification, and dilation of the pancreatic duct. According to a study by a group from the Mayo Clinic in 1989, atrophy and calcification of the pancreas and duct dilation were seen in 54%, 50%, and 68% of CP patients, respectively. MRI is more sensitive for diagnosing CP, and ductal abnormalities are specific and reliable signs of CP in MRI scans (Conwell et al. 2014; Luetmer et al. 1989).

Further evaluations such as endoscopic ultrasound (EUS) or endoscopic retrograde pancreatogram (ERP) are used once CP is highly suspected. EUS allows changes in the pancreatic parenchyma and pancreatic duct to be verified by placing a US probe in the stomach or duodenum. EUS criteria are based on ductal and parenchymal findings described by the International Working Group using minimum standard terminology (Catalano et al. 1998; Wallace et al. 2001; Wiersema and Wiersema 1995). ERP is not frequently used for diagnostic purposes because of its invasiveness (Conwell et al. 2014). ERP, however, is a sensitive procedure to detect small changes in the pancreatic duct, such as minor stenosis, because it provides a direct visualization of the duct. ERP is applicable for taking a cytological sample and for treating duct stenosis by implanting a stent. The most important concern in TPIAT is to confirm that the pancreatic disease is nonmalignant. Furthermore, ERP is used especially for pancreatic duct stenosis or suspicion of malignant disease to collect cytological or histological biopsies for evaluation. The diagnosis and etiological classification should be comprehensively and carefully done in CP, especially to distinguish CP from oncological disease.

Indication of TPIAT

TP is a radical treatment for CP. The final goal of TP is to attain relief from intractable pain. IAT is the replacement of beta cells to prevent surgical diabetes after TP. Thus, the final goal of TPIAT is to alleviate pain due to CP while retaining pancreatic endocrine function (Chinnakotla et al. 2014). Retaining any amount of pancreatic endocrine function greatly eliminates the occurrence of severe hypoglycemic episodes due to the complete absence of functional islets.

TPIAT is performed for carefully selected CP patients after failure of treatment with medication or endoscopic procedures. Indications of TPIAT are

Table 1 Inclusion and exclusion criteria for TPIAT at Baylor University Medical Center

Inclusion criteria	1. Diagnosed with chronic pancreatitis by a treating gastroenterologist or pancreatologist or other indications as jointly agreed upon by islet transplant surgeon and pancreatologist 2. Prior procedures (celiac block or pancreatic duct stents) that have failed or only provided temporary pain relief 3. Narcotic dependence for chronic pain due to pancreatitis 4. Self-reported poor quality of life with use of a formal scale 5. Ability to understand/give informed consent
Exclusion criteria	1. Known or suspected pancreatic malignancy 2. Portal hypertension or significant hepatic fibrosis 3. Cardiac contraindication to major abdominal operation 4. Pulmonary contraindication to major abdominal operation 5. Ongoing nonprescribed substance abuse, including alcohol 6. Profound uncorrected malnutrition 7. C-peptide negative during glucose tolerance test (may be directed for pancreatectomy without autotransplant) 8. Inability to understand/give informed consent

listed in Table 1. Current indications for TPIAT at Baylor University Medical Center include: (i) established diagnosis of CP by a pancreatologist or gastroenterologist, (ii) failure of maximal mediation and/or endoscopic procedures, (iii) severe abdominal pain that has led to narcotic dependence, and (iv) impaired quality of life due to CP. The CP patients who have the following major conditions are not considered for TPIAT: (i) known or suspected pancreatic malignancy, (ii) portal hypertension or significant hepatic fibrosis, (iii) cardiac or pulmonary contraindication to major abdominal operation, (iv) ongoing nonprescribed substance abuse including alcohol, (v) profound uncorrected malnutrition, (vi) C-peptide negative during glucose tolerance, and (vii) inability to understand/give informed consent. Of note, hepatic portal thrombosis is a major adverse event for islet infusion. For this reason, patients who have a risk of portal hypertension are excluded. Recent reports showed that patients with locally limited pancreatic malignancy or benign tumor have undergone TPIAT with successful outcomes (Balzano et al. 2014; Balzano et al. 2013; Yoon et al. 2014). Traumatic pancreatic injury is another indication for TPIAT (Jindal et al. 2010; Thakor et al. 2015).

Total pancreatectomy alone is performed in medical centers that do not have a dedicated facility to isolate functional pancreatic islets. According to previous studies, a large percentage of patients were readmitted for diabetic complications after TP.

Operative Procedure

Major aspects of the TPIAT procedure are shown in Fig. 1. Pancreatectomy is a complicated procedure. Sometimes severe adhesion between the pancreas and surrounding organs is evident, resulting in difficulty in recognizing major vessels connected to the organ. For surgery during pancreatitis attacks, it may be difficult to stop bleeding because of developing capillary vessels. Surgery during the acute phase of pancreatitis should be avoided as much as possible. After laparotomy, whole abdominal assessment is performed to eliminate the possibility of any other oncological disease. The hepatic and splenic flexures are mobilized, and stomach, duodenum, and pancreas head are retracted to the left side. A "wide Kocher maneuver" is performed to separate the head of the pancreas from the inferior vena cava and aorta and to separate the body-tail of the pancreas from the retroperitoneum (Heidt et al. 2007). The gastrocolic and hepatogastric ligaments are widely incised to expose the anterior surface of the pancreas. The third portion of the duodenum is separated from the Treitz ligament as transverse mesocolon. Next, the hepatoduodenal ligament is separated. The common bile duct, proper hepatic artery, and portal vein are identified, and the upper stream of the common bile duct is dissected. In the majority of cases, the gallbladder would have been resected in a previous surgery. The proper hepatic artery and common hepatic artery are divided from the pancreas. The gastroduodenal artery and the root of

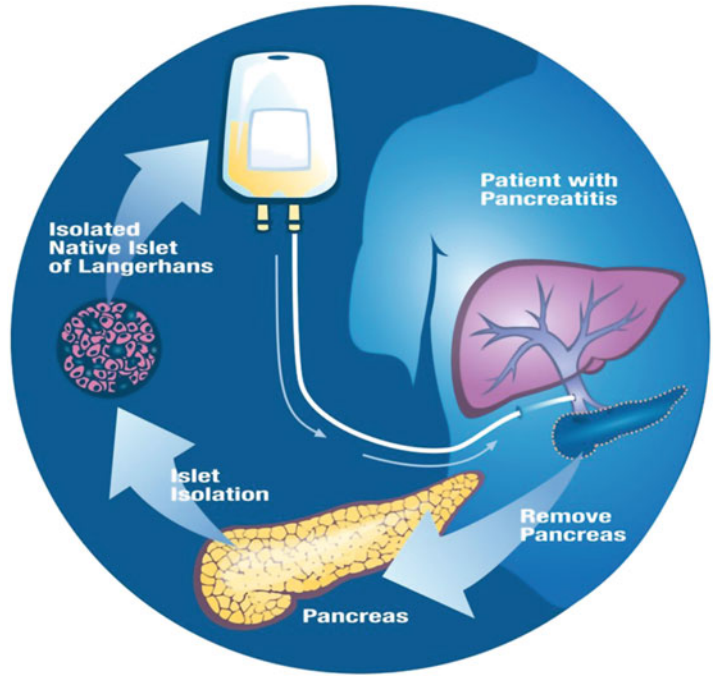

Fig. 1 Schematic representation of the TPIAT procedure for patients with chronic pancreatitis

the splenic artery are taped to preserve blood flow into the pancreas as long as possible, and the right gastric artery is cut. The distal side of end of gastroduodenal artery is cut after dissecting the right epigastric artery. Then, the transverse colon is retracted to the upper side, and the mesocolon and duodenum are separated. The jejunum is pulled to the right side after being cut with a linear stapler and retracting down the transverse colon. After that, the mesentery of the jejunum is cut, the uncus of the pancreas is separated from the superior mesenteric artery, and the inferior pancreaticoduodenal artery is cut. After separating the pancreas and portal vein, the splenic artery and vein are cut. The pancreas with the duodenum and spleen is removed after cutting the gastroduodenal artery.

In the majority of IAT centers, the pancreas is transported along with duodenum and spleen for islet isolation. In Baylor University Medical Center, specially trained islet specialists are involved in the organ procurement, trimming the organ, and performing pancreatic ductal cannulation. This procurement procedure is performed under cold condition for the purpose of shortening the warm ischemic time. The trimmed pancreas alone is placed in the cold preservation solution and transferred to an islet processing facility clean room. During the time of islet isolation, reconstruction is performed in the operating room, including choledochojejunostomy and duodenojejunostomy. Galvani et al. reported on a fully robotic-assisted TP followed by IAT, allowing safe vascular dissection and reconstruction of the digestive tract (Galvani et al. 2014; Gruessner et al. 2014).

Pancreatic Islet Isolation for Autologous Transplantation

Pancreatic islets occupy approximately 2–5% of the volume of the pancreas in healthy adults (Foulis 1993). The techniques of pancreatic islet isolation for clinical islet autotransplantation have been developed based on those designed for allogeneic islet transplantation using a brain-dead donor who has a healthy pancreas. The major components of the pancreatic islet isolation process consist of enzymatic digestion of the pancreas and optional density-gradient purification and assessment of isolated islets (Ricordi et al. 1989). The condition of the resected

pancreas is a critical factor in the outcome of islet isolation (Ricordi et al. 1989). Structural damage to the pancreatic tissue including severe fibrosis, calcification, and prior distal pancreatectomy are more commonly encountered during the assessment of pancreatic status in TPIAT than in the setting of a carefully chosen healthy donor pancreas for allogeneic transplantation. Each step involved in the islet isolation such as enzyme perfusion, pancreas digestion, and islet purification should be optimized for the individual CP patient. The technical approaches of islet isolation for clinical islet autotransplantation are presented below.

Enzyme Perfusion into Chronically Inflamed Pancreas

After decontamination of the procured pancreas with polyvinylpyrrolidone, antibiotics, and/or antifungal drugs followed by extensive washing with Hank's Balanced Salt Solution (HBSS), perfusion of collagenase enzyme is the first step of pancreatic islet isolation (Bucher et al. 2005). In a pancreas with minimal change due to CP, the pancreatic duct system should be maintained intact and collagenase solution can be distributed into the whole pancreas as in a healthy organ. Many islet institutes have implemented semiautomated enzyme perfusion with a peristaltic pump for 10 min in cold temperature to prevent premature activation of the collagenase enzyme. Optional manual injection of collagenase solution into the pancreas parenchyma is considered for severely fibrotic organs when distension of the pancreas during the semiautomatic enzyme perfusion is not sufficient. For this reason, the distension of the pancreas during enzyme perfusion should be carefully monitored and recorded to evaluate the quality of enzyme distribution (Sakuma et al. 2008; Takita et al. 2010).

Of note, several collagenase enzymes are commercially available for pancreas digestion in clinical islet autotransplantation. A mixture of collagenase derived from *Clostridium histolyticum* (Ch) and neutral protease(s) derived from the same microorganism or *Bacillus thermoproteolyticus rokko* are commonly used. Balamurugan et al. determined the efficacy of different combinations of collagenase and neutral proteases for clinical islet autotransplantation. They showed that the isolated islet yield was maximized when intact class 1 collagenase and neutral protease with Ch was used (Balamurugan et al. 2012).

Digestion of Pancreas

The pancreas perfused with cold collagenase enzyme is cut into approximately 9–11 small pieces of 2–4 cm length before the digestion process. The pieces of pancreas and the enzyme solution are placed in the Ricordi chamber. The pancreatic tissue is digested with activated collagenase during circulation in a closed circuit with a Ricordi chamber and a warm water bath. The digestion temperature is maintained between 30 °C and 37 °C. Light marbles in the Ricordi chamber exert mechanical force to aid the digestion process. At regular intervals of 2–4 min apart, an aliquot of the enzyme solution is used to measure released islets. The enzymatic digestion of the pancreas is discontinued after optimal release of islets is observed in the test samples. In the case of a severely damaged pancreas, the number of islets released may be less than that for a normal organ. Digestion time is determined based on both microscopic observation of digested tissue samples and macro changes in the size of the pancreatic mass in the Ricordi Chamber. Technical experience of the team involved in the isolation process is critical for successful isolation of high-quality islets.

Optional Islet Purification

The purpose of IAT is to return as many of a patient's own islets as possible to maximize the opportunity to retain pancreatic endocrine function. At the completion of the enzymatic digestion of the pancreas, it is common to obtain a compacted cell volume of greater than 20 ml. Since infusion of a large volume of packed pancreatic tissue into the liver could result in portal vein thrombosis, it is essential to purify islets from the whole digest. Islet purification is an optional procedure since a significant mass of islets can be lost during the purification process. The

University of Minnesota group has reported that the final tissue volume that is transplanted is an independent predictor for the elevation of portal vein pressure during islet infusion. They proposed a target tissue volume of less than 0.25 ml/kg of patient body weight (Wilhelm et al. 2013).

Islets are purified using a density gradient centrifugation method and a cell separator such as a COBE 2991 processor. After the centrifugation, islets and acinar cells are distributed in lighter and heavier density layers, respectively. Some islet transplant centers use islet purification with a fixed density of high- and low-gradient solution, while others employ purification with a continuous gradient solution after adjusting for the optimal density of each pancreatic digest (Anazawa et al. 2011). The benefit of islet purification with density-adjusted continuous gradient solution is to minimize islet loss. A significant benefit of islet purification is the elimination of acinar tissue, which is known to negatively impact islet function.

Remote Site Processing

Pancreases of CP patients exhibit large variation from minimal change from healthy to severely fibrotic "rock-like" pancreases. Some patients with CP have a history of previous pancreatic surgery such as Peustow's procedure, Whipple procedure, and distal pancreatectomy before TPIAT. Every islet isolation procedure in clinical islet autotransplantation should be customized for each patient based on the above description. Hence, well-experienced islet specialists should be in charge of the isolation process. From a regulatory point of view, the current good tissue practice (cGTP) has to be followed during the entire tissue manufacturing process. As a result, access to islet isolation facility is limited. The remote site processing is an alternative way to broaden the opportunity of TPIAT to patients with severe CP who are not at an islet isolation facility. A fruitful collaboration between the University of California at Los Angeles for surgery and University of California at San Francisco for islet isolation was recently reported (Tai et al. 2014).

Islet Infusion

Islet Infusion into Hepatic Portal Vein

The isolated islets are suspended in sterile transplant medium and packed in a specially designed infusion bag along with a low dose of heparin (70 units/kg body weight of the patient). The bag method is a commonly performed procedure for islet infusion into the hepatic portal vein since the infusion rate is manageable during continuous natural dripping by gravity. Elevation of portal vein pressure to excessive levels (>22 mmHg) can be prevented by reducing or temporal discontinuation of islet infusion. Portal vein pressure should be carefully monitored during the infusion. During the early years of TPIAT procedures, isolated islets were placed in a syringe and directly injected into the portal vein. This approach carried a risk of unintended high portal vein pressure.

Route of Islet Infusion

Several routes are available for autologous islet infusion into the hepatic portal vein. The common route is cannulation into the portal vein from the superior mesenteric vein branch before skin closure. Transhepatic cannulation with interventional radiology after the operation is an alternative way. The University Hospitals of Leicester has reported a new approach of islet infusion using the umbilical vein (Ong et al. 2009).

Peritransplant survival of islet autograft

Following transhepatic intraportal infusion of islets, a strong nonspecific inflammatory response has been shown to occur in TPIAT patients (Naziruddin et al. 2014a). This response has been termed as "instant blood-mediated inflammatory response" (IBMIR) and is primarily triggered due to the incompatibility between isolated islets and blood. Mechanisms underlying this damaging response are unclear. It has been shown that IBMIR in TPIAT patients is

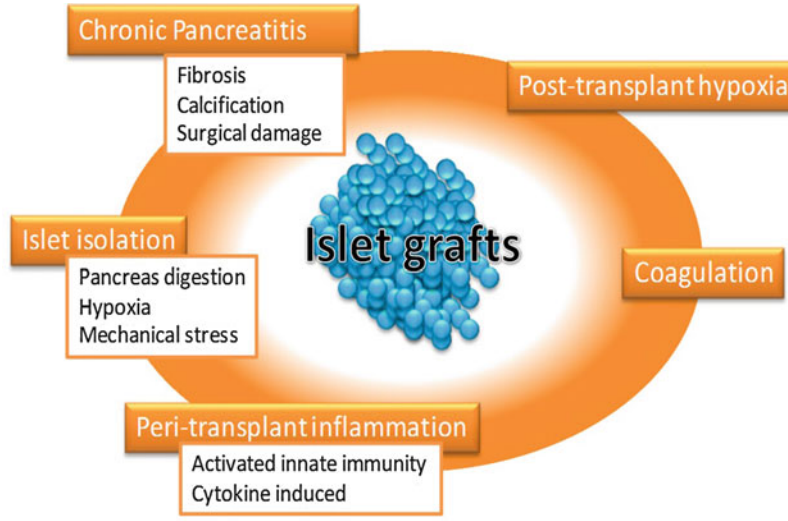

Fig. 2 Factors that influence quality, quantity, function, and survival of islets in TPIAT

characterized by concomitant release of inflammatory mediators (such as TAT, IL-6, IL-8 and IP-10) and C-peptide. When islets were mixed with autologous blood under in vitro conditions, expression of MCP-1 increased dramatically in the islets, indicating its significant role as a mediator of islet damage (Kanak et al. 2014a). Furthermore, islets infused into liver experience other damaging events (illustrated in Fig. 2), which include hypoxia, oxidative stress, and proinflammatory response (Kanak et al. 2014b).

Clinical Outcome

The main purposes of TPIAT are to eliminate intractable abdominal pain by total pancreatectomy, to preserve pancreatic endocrine function by returning autologous islets, and in turn, to improve the quality of life of CP patients. Several reports from IAT centers have been published to show their clinical results. Table 2 provides a summary of data from major TPIAT centers.

Patient Survival

According to the University of Minnesota, which has performed more TPIAT than any other center, the five-year survival rate after surgery was 90% including adults and children (n=409) (Sutherland et al. 2012). The Leicester group reported that survival rate after TPIAT was significantly longer than total pancreatectomy alone although the clinical study is not a randomized trial (16.5 and 12.9 years in TPIAT and TP-alone groups, respectively $p < 0.01$) (Garcea et al. 2013).

Impact of TPIAT in Endocrine Function

A major purpose of IAT is to return as many of the patient's own pancreatic islet cells as possible to the patient. The amount of islets transplanted, assessed by islet equivalents (IEQ), has been reported to correlate with glycemic control after TPIAT. Sutherland et al. reported that the proportions of recipients who achieved insulin independence one year after TPIAT are 7%, 27%, and 63% for recipients who were transplanted with less than 2500 IEQ/kg, 2500–5000 IEQ/kg, and more than 5000 IEQ/kg, respectively (Sutherland et al. 2008).

Pain control

Elimination of severe abdominal pain is the major advantage of TP. Major centers have reported that

Table 2 Summary of current outcomes of TPIAT

Center	Pain outcome	Diabetes outcome
University of Minnesota (Sutherland et al. 2012)	59% became narcotic free 24 months after TPIAT although all patients were narcotic dependent before TPIAT	22% achieved insulin independence 36 months after TPIAT if the patients received 2500–5000 IE/kg
University of Cincinnati (Wilson et al. 2013)	79% became narcotic free 9 months after TPIAT	29% achieved insulin independence 9 months after TPIAT (mean islet dose: 7437 IEQ/kg)
University of Alabama (Argo et al. 2008)	60% became narcotic free 6 months after TPIAT	No patient achieved insulin independence 6 months after TPIAT (mean islet dose: 1551 IEQ/kg)
Medical University of South Carolina (Morgan et al. 2012)	23% became narcotic free 12 months after TPIAT	24% achieved insulin independence 12 months after TPIAT (mean islet dose: not reported)
University Hospital of Leicester (Garcea et al. 2009, 2013)	42% became narcotic free 60 months after TPIAT	24% achieved insulin independence 12 months after TPIAT (mean islet dose: not reported)
Baylor (Naziruddin et al. 2014b)	70% became narcotic free 12 months after TPIAT	35% achieved insulin free 12 months after TPIAT (mean islet dose: 5438 IEQ/kg)

more than half of the patients became narcotic independent although there is variation in the results between institutes performing TP (Table 2). Long-term follow-up is warranted to justify pain outcomes since pain due to the surgical procedure, including skin incision, can affect the results.

Conclusion

TPIAT has shown tremendous promise for the treatment of patients with severe CP not only in terms of achieving relief from intractable pain but also for prevention of surgically induced diabetes. Improvements in the assessment of CP severity based on laboratory tests, image analysis, and a multidisciplinary team have played a central role in the selection of appropriate candidates for TPIAT. Development of unified criteria for early diagnosis and treatment will minimize pancreatic damage, which in turn will lead to better results with the islet isolation process and improved transplant outcome. The process of isolating islets is undergoing subtle changes to improve the mass of isolated islets. These include improving the pancreas procurement and preservation steps, purification of islets using islet-friendly gradient solutions, and incorporation of anti-inflammatory solutions. While the liver is the site most commonly used for islet autotransplantation, several hurdles remain to be overcome to improve survival of transplanted islets. These include minimization of damage due to IBMIR, hypoxia, endoplasmic reticulum stress, and islet exhaustion. Since the isolation procedure requires technical expertise and adherence to cGTP conditions, the practice of TPIAT is still limited to select centers. The introduction of potent anti-inflammatory therapy at least during the peritransplant period should improve islet survival. A major objective of the TPIAT procedure is to improve the quality of life (QoL) of CP patients, and several published reports have already indicated significant improvement in the QoL of TPIAT patients. However, a comprehensive multicenter trial is essential to draw firm conclusions. Finally, the cost of TPIAT is considered prohibitive for its broader application to many qualified patients. Policies that will make it affordable and thus increase the number of TPIAT surgical procedures will also lead to the development of innovative approaches to further significantly improve the outcomes.

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