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# Islet autotransplantation: past, present and future. Chapter I: chronic pancreatitis: pathogenesis, indications and treatment



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## Practice points

- Chronic pancreatitis (CP) a progressive disease characterized by an irreversible damage to the pancreas.
- CP is associated with varying degrees of inflammation, fibrosis, exocrine and endocrine tissue insufficiency, and pancreatic sclerosis.
- The exact pathogenesis of CP is unknown, but a number of different risk factors have been associated with the development of the disease.
- The goals of treatment are to manage the disease process to prevent recurrent attacks; relieve acute or chronic pain; correct metabolic consequences of pancreatic sclerosis and fibrosis, and exocrine and endocrine insufficiency; manage complications when these arise; and address psychological problems that develop over time.
- As the disease progresses, supportive therapy becomes ineffective and can no longer relieve the progressive chronic pain associated with CP.
- Approximately 50% of the patients living with CP undergo either near-total pancreatectomy (near-TP) or total pancreatectomy (TP).
- The goal of near-TP or TP is to alleviate the intractable pain inflicted by CP in patients who fail other forms of treatment approaches.
- However, surgery is considered to be a treatment of last resort, only after all other treatment modalities – both surgical and nonsurgical – fail to improve clinical prognosis.
- Near-TP and TP result in serious metabolic abnormalities such as insulin and glucagon deficiency, as well as surgically induced insulin-dependent pancreatogenic diabetes (PD) with poor metabolic control.
- Surgery-induced metabolic abnormalities are often difficult to manage. Patients who have PD may have wide daily glycemic excursions and unpredictable hypoglycemia due to endocrine failure and exocrine deficiency.
- These complications severely limit the utility of surgical interventions, unless islet autotransplantation (IAT) is utilized to rescue the patient from PD.

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**Practice points (cont.)**

- IAT following pancreatic resection has been demonstrated to improve pain, alleviate the risk of ‘brittle diabetes’ and offer freedom from exogenous insulin in a large number of patients.
- Studies show that IAT after TP results in a significant improvement in quality of life in patients with CP.
- Given a longer life expectancy and favorable results achieved following IAT after near-TP or TP, IAT represents a viable therapeutic alternative for a wide range of glycemic disorders in an extended range of population that includes young children and elderly patients.
- Specific biomarkers in conjunction with noninvasive imaging studies are needed to correlate pathology of the pancreas to the islet isolation yield, and consequently IAT outcome.

**SUMMARY** The most successful islet transplants have been performed in non-autoimmune diabetes patients, in an autologous setting, in conjunction with total or near-total pancreatectomy for the treatment of pancreatic or hepatobiliary conditions. The primary goals are the treatment of an underlying disease and relief of persistent pain. Islet autotransplantation is important in this setting. Following islet autotransplantation, most patients maintain good glycemic control, with ~30–40% able to discontinue insulin therapy. Transplantation of high islet mass is associated with higher C-peptide, in-range HbA1c and insulin independence. Strategies to increase the proportion of insulin-independent patients and long-term engraftment include islet isolation, curtailing the innate immunity-associated events and beta-cell apoptosis, and alternative transplant sites. Future studies are of benefit. Chapter one reviews the pathogenesis, indications and treatment of chronic pancreatitis.

**KEYWORDS**

- chronic pancreatitis
- diabetes • insulin
- islet autotransplantation
- pancreatectomy
- transplant

This is the first chapter of the two-part review that covers past experiences and future directions of islet autotransplantation (IAT) for the treatment of chronic pancreatitis (CP) and other pancreatic disorders [1].

CP is characterized by a progressive, irreversible damage to the pancreas and is associated with varying degrees of inflammation, fibrosis, exocrine and endocrine tissue insufficiency, and pancreatic sclerosis. Although the exact pathogenesis of CP is unknown, a number of different risk factors have been associated with the development of the disease. These include alcoholism; hepatobiliary disease; endogenous, genetic and idiopathic factors; infection; neoplasms; and acute recurring pancreatitis. It has been estimated that 90–95% of adult patients with CP have alcoholic or idiopathic disease. With multiple factors contributing to the development of CP, there is no clear consensus as to whether these interact to contribute to the development of the disease. As a result, to date treatment for CP is largely empirical. The goals of treatment are to manage the disease process to prevent recurrent attacks; relieve acute or chronic pain; correct metabolic consequences of pancreatic sclerosis and fibrosis, and exocrine and endocrine insufficiency; manage complications when these arise; and address psychological problems that develop over time.

With time, available supportive therapy becomes ineffective and can no longer relieve the progressive chronic pain associated with CP. This forces approximately 50% of the patients living with CP into the care of the surgeon for consideration of near-total pancreatectomy (near-TP) or total pancreatectomy (TP) [2].

The goal of near-TP or TP is to alleviate the intractable pain inflicted by CP in patients who fail other forms of treatment approaches. However, both are utilized as the treatment of last resort, only after all other treatment modalities – both surgical and nonsurgical – fail to improve clinical prognosis. Near-TP and TP alone result in serious metabolic abnormalities such as insulin and glucagon deficiency, as well as surgically induced insulin-dependent pancreatogenic diabetes (PD) with poor metabolic control. Both, the glucagon deficiency and poor metabolic control are often difficult to manage. Patients who have PD (also known as ‘iatrogenic diabetes’) may have wide daily glycemic excursions and unpredictable hypoglycemia not only due to endocrine failure, but also exocrine deficiency [3]. Hence, although improved morbidity and mortality as a consequence of pancreatic resection and/or TP have been demonstrated, complications discussed above severely limit the utility of surgical interventions [3].

IAT offers a valuable addition to the surgical resection of the pancreas for the treatment of CP and other rare pancreatic disorders. IAT following pancreatic resection has been demonstrated to improve pain, alleviate the risk of 'brittle diabetes', and offer freedom from exogenous insulin in a large number of patients. A number of studies clearly show that IAT after results in a significant improvement in quality of life (QOL) in patients with CP. Given a longer life expectancy and favorable results achieved following IAT after pancreatic resection or TP, IAT represents a viable therapeutic alternative for a wide range of glycemic disorders in an extended range of population that includes young children and elderly patients. Badly needed at this point are the assessment tools that would have a predictive value that correlates the pathology of the pancreas prior to pancreatic resection or TP to the islet yield, and, consequently, to IAT outcome. These can include noninvasive imaging studies or biomarkers specific for the pancreatic milieu, or both. Although some work in this area has been done, more studies are required to move the field forward.

The merits of IAT following pancreatic resection or TP will be discussed in Chapter II of this manuscript.

### Indications

TP with IAT was first performed in 1977 at the University of Minnesota (UMN), as a treatment modality for CP [4]. From then on, it has been used almost exclusively in patients undergoing pancreatectomy as a result of intractable CP. Severe complications after pancreatic surgery such as pancreatic fistula that requires re-laparotomy with left pancreatectomy, or complete pancreatectomy and patients with high-risk pancreatic stump, are also indications for IAT. Recently, the application of IAT has been extended to patients who present with the loss of pancreatic parenchyma as a consequence of the resection of focal benign processes including pancreatic pseudocysts, insulinomas, neuroendocrine tumors and other neoplasms, intrapapillary mucinous neoplasms, pancreatectomy after severe trauma, and some other rare conditions [5–8].

#### • Chronic pancreatitis

CP is a benign inflammatory condition, in which the development of fibrosis and destruction of the pancreatic parenchyma lead to an irreversible and sometimes severe damage to endocrine and

exocrine pancreatic functions [2,9–11]. Increased lifetime risk of adenocarcinoma in some CP patients has been well established [12]. Clinical manifestations of CP vary as to the degree of pain, loss of exocrine function and occurrence of glucose abnormalities. The main goal of surgical treatment for CP is to relieve intractable pain in patients that fail all prior medical, endoscopic and surgical therapeutic approaches [13]. Pain associated with CP is often intractable and debilitating; its pathogenesis includes ischemia, intrapancreatic hypertension, neurogenic alterations of the pancreatic nerves and stenosis of the common bile duct or duodenum [14,15].

Traditionally, acute pancreatitis (AP) and CP have been considered fundamentally different, with AP resulting in full clinical recovery and a return to a normal pancreatic parenchyma. However, at the present time AP, recurring AP and CP are considered as 'a disease continuum' [2,15]. There are several reasons for this opinion change: although CP can ensue without any prior episodes of AP, recurring AP can develop into CP very rapidly and/or over time; all three conditions share overlapping genetic and environmental causative factors, as well as pathogenic origins; all three conditions have similar clinical presentation, that is, severe abdominal pain, inflammatory changes, and increased blood amylase, lipase and trypsinogen levels [2,15].

It has been proposed that the sentinel event in the development of pancreatitis is the pancreastasis, or inability of the pancreatic acinar cell to release the newly synthesized, activated digestive enzyme. This results in significant inflammation of the pancreatic parenchyma. Although not proven to date, it is possible that this exocytosis blockade is due to some sort of injury or oxidative stress event. It has been postulated that it is the unregulated trypsinogen activity in the acinar cell which leads to the first AP attack. If this event is sufficiently severe it results in the activation and recruitment of tissue macrophages and subsequent damage to the pancreatic parenchyma by a number of underlying causative factors. These events eventually lead to fibrosis via macrophage-mediated stellate cells in the acinar tissue. Regardless of the etiology, CP is the result of progressive pancreatic damage caused by recurring episodes of pancreatic inflammation. This results in a progressive atrophy of the acinar tissue, increased mononuclear cell infiltration, varying degree of distorted or blocked ducts, acute and chronic inflammation,

and fibrosis. In different individuals, progression of CP to end-stage fibrosis occurs without any degree of predictability [2,15–16].

Initially, alcohol abuse was considered to be the most common underlying cause of CP not only in the US, but also around the world; over the last few years this perception has slowly changed. Recent studies conducted in Europe and US have demonstrated that alcoholism is a contributing factor in only 34% of the cases of CP in Italy and 44% of the cases in the USA [2]. Ahmed *et al.* reported that out of a cohort of the first 135 patients treated for CP at UMN, only 16% of the cases were attributed to alcohol abuse, with 60% of the cases described as idiopathic [17]. Additionally, cigarette smoking; exposure to occupational volatile hydrocarbons; certain drugs such as valproate, phenacetin, estrogen, thiazide and azathioprine; endogenous factors such as chronic renal failure, gall stones, hypercalcemia and hypertriglyceridemia; infections; inherited germline mutations; autoimmune events; ductal obstruction and trauma and sphincter of Oddi dysfunction are also considered to be important risk factors [2,15,17].

The diagnosis of CP is based on associated symptoms, imaging studies and laboratory tests that include but are not limited to lipid and calcium profiles, serological evaluation and liver function tests; the diagnosis is difficult, with a number of tests returning false positive results [2]. Computed tomography, endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography and endoscopic ultrasound are helpful imaging techniques in detecting pancreatic ductal and textural abnormalities [18]. The final test might utilize a biopsy specimen at the time of pancreatectomy, although a conclusive diagnosis can be made much earlier in the course of the disease [2,15,18].

Clinical management of patients diagnosed with CP is aimed at relieving retractable pain, preventing recurring attacks, managing metabolic consequences such as diabetes and addressing patient's QOL. Lifestyle and dietary changes, such as cessation of alcohol and smoking, as well as diet adjustments, are the baseline of clinical management for CP and should be addressed before progressing to more radical treatment approaches [19]. Drug therapy for the treatment of underlying conditions for abdominal pain, such as biliary and gastric outlet obstruction, pseudocysts, and malignancies, should be also considered before debating endoscopic

treatment, or pancreatectomy as a possible treatment option [20]. Pancreatic enzyme supplements have been successfully utilized in small duct disease patients and are recommended for CP patients; the enzyme dose should be based on patient's diet and fat intake [2,15,21].

Pain in CP occurs with or without ductal obstruction; its severity is not always correlated with the extent of morphological changes in the pancreatic parenchyma, or progression of the disease. Sutherland *et al.* reported intractable pain in patients with either minimal or severe morphological changes in the pancreas [15]. Many of the patients need analgesics, both non-opioids and opioids, although initial treatment should include nonsteroidal anti-inflammatory preparations followed by mild opioids. Although opioid addiction is a consideration in CP patients, the first priority in CP patients with retractable is pain management [22]. Patients who require continuous and recurring opioid analgesics for pain relief are candidates for invasive procedures. Endoscopic therapy has been utilized to treat pancreatic duct, biliary obstruction, or pseudocyst drainage. When all available medical and more invasive (endoscopic) approaches fail, pancreatic resection is the next step to be considered in cases of persistent and/or recurring CP pain [2,15].

#### • Benign & malignant neoplasms

Environmental and genetic risk factors have been implicated as contributing factors in the development of AP, CP, as well as pancreatic ductal adenocarcinoma (PDAC). Furthermore, both common CP and inherited pancreatitis are well-known risk factors for PDAC [23]. At the same time, PDAC also causes AP and CP. Likewise, although long-standing diabetes increases the risk for PDAC, the latter itself causes glucose intolerance and diabetes as a paraneoplastic process [24]. Hereditary pancreatitis with a rare mutation of the cationic trypsinogen gene (PRSS1) has an exceptionally high risk of development of this type of neoplasm. Patients with hereditary pancreatitis have a 50-times greater risk of developing PDAC compared with the corresponding background population, with the lifetime risk for developing PDAC of about 70% [24–26].

At centers in which IAT is performed for diseases other than CP, the absolute histopathologic diagnosis of a benign condition is necessary prior to the islet isolation procedure [27]. *Arch. et al.*

advocates that a malignant disease should not be considered as exclusion criteria for IAT [27]. It has been long established that although the goal of islet isolation is the enrichment of the endocrine fraction, that is, islet cells, a certain percentage of ductal cells can be found in almost every islet cell preparation. To minimize the risk of disseminating malignant cells with IAT, the authors suggest the use of a multilevel safety strategy. First, multifocal pancreatic disease should be excluded preoperatively, based on various imaging techniques, including MRI and/or endoscopic ultrasonography (EUS) performed on a case-by-case basis. Second, the multifocal pancreatic disease should be excluded at the pancreatic margin during the surgical procedure. Third, 1 cm of the remaining pancreatic tissue near the pancreatic margin should be removed. Fourth, a purification step during the islet isolation procedure to purify the endocrine (islet) tissue from the exocrine component must be performed [27].

The literature indicates that the multifocality of pancreatic adenocarcinoma is not as common as it was first thought. Confirming previously published data, Kloppel *et al.* reported that multicentric adenocarcinoma *in situ* and/or invasive adenocarcinoma were not as common as first thought, and occurred in only 5–10% of the cases, in the cohort of 37 patients [28]. The authors concluded that IAT in patients with CP and borderline pancreatic adenocarcinoma was not only possible, but did not seem to contribute to the dissemination of the neoplastic lesion following pancreatic resection and IAT. Additional reports indicate that none of the patients that underwent pancreatic resection and IAT for various types of pancreatic neoplasms demonstrated any evidence of liver metastases related to IAT, at 3–30 month follow-up [29–31]. Additionally, it has been demonstrated that patients with multifocal intrapancreatic neoplasms that underwent IAT immediately after pancreatic resection demonstrated no evidence of recurrence of metastatic disease in the liver [5,32].

Patients presenting with benign neoplasms are candidates for IAT as well. A single-center experience with IAT after extensive pancreatic resection in several patients with benign tumors of the pancreas was reported to achieve good islet yields and insulin independence compared with the results observed in patients with CP. The authors indicated that IAT should be considered when extensive pancreatectomy is required for resection of a benign tumor [5].

IAT in patients presenting with pancreatic malignancy and intrapancreatic multifocal neoplasms is still considered a major controversy. AIT in these cases should be considered in terms of a risk/benefit ratio, with numerous studies to clarify the issue. Shapiro *et al.*, however, demonstrated the success of pancreatic resection with IAT in an elderly patient diagnosed with the metastatic renal cell carcinoma, with multifocal metastasis to the liver and pancreas [33].

Detail literature review on this subjects seems to indicate that considering the fact that IAT is a relatively simple, safe and effective procedure that results in the amelioration of surgically induced diabetes; collaboration with facilities able to effectively isolate and prepare high-quality islet preparations is relatively easy, IAT should be seriously considered in patients with multifocal neoplastic conditions.

#### • Severe trauma & other rare conditions

Pancreatic trauma as a result of abdominal injury remains relatively uncommon [34]; it does pose a formidable challenge to the surgeon. Failure to manage such cases correctly may have devastating consequences. Penetrating trauma can be caused by stab or gunshot wounds, while blunt trauma occurs as a result of a motor vehicle, bicycle or pedestrian accidents, and are normally associated with liver and small bowel injuries. These types of injuries are sometimes difficult to visualize; hence, exploratory surgery within 12–24 h of injury becomes necessary [35]. While some pancreatic injuries can be treated with an external drainage, TP is the only option for most patients, mostly due to the extent of the injury [35]. It has been reported that surgically induced diabetes is a definite risk in trauma patients, and occurs in 8–50% of patients depending on how much pancreas is resected, and the extent of an underlying disease, if any. To prevent the development of surgically induced diabetes, IAT has been utilized after pancreatic resection to treat sustained injury to the pancreas, with reported success. Khan *et al.* described islet isolation performed on a remnant of the pancreas (63.5 g) removed from a 21-year-old service man critically wounded with multiple abdominal gunshot wounds while serving in Afghanistan [36]. The patient underwent a traumatic Whipple pancreatectomy, after which the remnant of the pancreas was shipped from Walter Reed Army Medical Center in Washington DC to the Diabetes Research Institute at the University



of Miami for islet isolation. The islets (221,250 islet equivalents [IEQ], with 40% purity and 90% viability) recovered during islet isolation – performed using the Ricordi automated method – were shipped back for IAT immediately after the isolation, under appropriate conditions [37]. The authors reported immediate function as assessed by an elevated C-peptide followed by insulin independence with near normal glucose tolerance test 1 and 2 months following surgery. Garraway *et al.* also reported two cases of IAT after distal pancreatectomy for trauma to the pancreas, one as a consequence of a car accident, and the second one following stabbing [38]. Although both of the patients required some insulin postoperatively, the first one became insulin independent 3 weeks following IAT, with the second patient's requirements ceasing very quickly following his transplant [38]. The data discussed above clearly indicate that IAT is a viable option for the prevention of surgically induced diabetes in a small group of patients requiring surgical intervention to avoid significant morbidity and mortality as a result of pancreatic trauma.

Pancreatic autologous islets were also demonstrated to successfully alleviate surgically induced diabetes after TP, in a 16-year-old patient with intractable pain, which was due to CP and primary sclerosing cholangitis. Over the 18-month follow-up, the patient did not show any progression of chronic liver disease or signs of portal fibrosis. The patient was weaned off pain medication over 12 months of post-transplant period, at which time glycemic control was reported as excellent without any need for exogenous insulin supplementation [39].

Artery venous malformation is another rare condition that leads to CP; it is defined as a vascular anomaly and a tumorous lesion. Three cases with artery venous malformation were reported in Japan. All three patients underwent a two-step procedure for TP, followed by intraportal IAT; with two patients reporting favorable outcomes. At the same time, the third patient's islet cell infusion could not be completed due to general complications some of which were associated with the islet cell infusion [40]. These results might be indicative of the fact that IAT in patients presenting with rare pancreatic conditions is not only possible, but can be beneficial, provided that the necessary care is taken to avoid exacerbating the patient's general condition. Islet cells designated for infusion in such cases should be purified to

limit the volume of the islet preparation and reduce the amount of acinar tissue infused.

• **Patient selection for pancreatic resection & islet transplantation**

The severity of gross morphology in CP subjects, as determined by imaging studies, does not necessarily correlate with the degree of pain experienced by the patient. Nor do the near normal or normal imaging studies rule out CP. Two types of CP have been described: early onset where pain precedes the development of gross pathologic changes and late onset where gross changes are detectable by the time the patient presents with pain [16].

Usually, CP diagnosis is made based on the EUS and/or histological findings. However, in patients undergoing TP-IAT, correlation between EUS and histology findings, especially in minimal change CP, is poor. Studies show that normal EUS cannot exclude minimal change CP, and abnormal EUS is not sufficient to make an unequivocal diagnosis [16]. Additionally, clinical course of CP is equally important for diagnosis, and should be considered. If the clinical progression of the disease fits the pain pattern of CP, diagnosis should be made based on clinical observations.

Regardless of the course of diagnosis, by the time patients are referred for surgery, they have already undergone metabolic assessment for endocrine and exocrine functions of the pancreas, imaging studies like computed tomography, MRI, laparoscopy, endoscopic retrograde cholangiopancreatography and endoscopic ultrasound [41]. The main centers performing pancreatic resection and/or TP for CP have adopted a multidisciplinary team approach in the patient selection process. In Leicester, for example, the multidisciplinary team consists of a pancreatic surgeon, a gastroenterologist, a pain specialist, a diabetologist, an anesthetist and a medical psychologist.

According to the published reports, UMN and the University of Leicester perform TP-IAT in CP patients who have intractable pain, regardless of the fact whether gross morphologic changes detected in the pancreas are minimal or severe. While IAT is not recommended for patients with an already impaired glucose tolerance, diabetic patients with clearly identifiable beta-cell function – as determined by a positive C-peptide – do undergo IAT with the aim of preserving metabolic function, improving metabolic control and

decreasing the rate of long-term diabetes complications [15,41–42]. Additionally, patients who abuse alcohol and illegal drugs, and have poorly controlled mental state, are normally excluded from the cohort of patients for whom IAT is recommended [41,42]. Recently, Dunderdale *et al.* described poor islet isolation outcomes in terms of low islet yield, higher exogenous insulin requirements, lack of improvement in pain scores and little improvement in long-term QOL after TP-IAP, mainly due to the condition of the pancreas at the time of diagnosis. These results compared quite poorly with those obtained in patients with nonalcoholic CP. The authors suggested that further studies are needed to define criteria for pancreatic resection and IAT in patients diagnosed with chronic alcoholic pancreatitis [43].

Patients diagnosed with acute recurrent pancreatitis, characterized by frequent and disruptive painful attacks, have been also considered as candidates for TP-IAT. Acute recurrent pancreatitis may, in some cases, lead to CP; patients devoid of any pain between episodes can develop interval pain or develop persistent pain. In such cases TP is recommended to ameliorate the persistent pain, and eliminate the need for opioid analgesia used to treat the persistent pain [15].

Although TP has been performed in patients presenting with pancreatic neoplasms, Canadian Diabetes Association Clinical Practice Guidelines Expert Committee recommends IAT to individuals undergoing TP for benign pancreatic disease only, provided that the islet isolation is performed at an experienced islet transplant center [44]. Recently, the indication for IAT after pancreatic resection has been extended to pancreatic diseases of malignant origin with encouraging results [33,45–46]. However, IAT in this cohort of patients is still considered a major controversy. As discussed elsewhere in this chapter, additional data are needed to define the criteria for performing IAT applicable to such cases. The main concern in this patient population is the risk of dissemination of the malignant neoplasm following IAT. However, to date no such cases have been reported.

#### • **Assessment prior to pancreatic resection & islet autotransplant**

Although IAT is capable of preserving endocrine function and improve PD following pancreatic resection, much uncertainty is associated with the diabetes outcomes for individual patients.

It is dependent on timing of TP-IAT, balance between preservation of islet cell mass proceeding with the surgery during the later stages of the disease and the islet mass available at the time of IAT. The latter is hard to predict prior to TP.

According to the published reports, approximately one-third of adult IAT recipients are insulin independent, with another one-third on minimal exogenous insulin. The remaining one-third requires basal-bolus insulin, with approximately 10% of these patients testing negative for C-peptide [47]. It has been proposed that the likelihood of IAT success depends largely on the outcome of the islet isolation procedure prior to IAT. Sutherland *et al.* reported that out of 409 TP-AIT patients he followed, islet yields of <2500 IEQ/kg resulted in insulin independence in only 12% of the patients over 3-year follow-up, compared with 2501–5000 IEQ/kg and >5000 IEQ/kg islet doses that lead to insulin independence in 22 and 72% of the patients, respectively [42]. Regardless of the insulin dose, the majority of the patients who received a moderate number of islet cells have a favorable metabolic outcome; nearly all patients demonstrate graft function as assessed by C-peptide positivity, with the majority maintaining hemoglobin A1c (HbA<sub>1c</sub>) levels in the range of <7% [42].

Prior pancreatic surgery and atrophy of the pancreatic parenchyma have been reported to negatively impact the islet isolation yield, although this relationship is not always consistent. The literature regarding islet isolation outcomes from deceased donors and porcine islet isolations indicates strong correlation between islet isolation outcome and insulin secretory capacity, the acute insulin response to arginine or glucose, in particular. However, this relationship remains largely unexplored in TP-IAT patients.

Preliminary data suggest that there might be correlation between C-peptide levels obtained by mixed meal tolerance testing and islet isolation yield [48]. Lundberg *et al.* investigated whether preoperative metabolic testing had any value in predicting islet isolation yield, and could lead to improved assessment of TP-IAT candidates [47]. The relationship between intravenous glucose tolerance test, mixed meal tolerance test (MMTT) and islet mass in 60 adult patients was explored using the multivariate logistic regression model. The authors reported that stimulated insulin and C-peptide levels, as well as glycemic measures obtained preoperatively,

had a weak correlation with the number of IEQ in the final product (final product of the islet isolation process), as well as IEQ/kg of recipient body weight (final product IEQ/kg). Although these data confirmed earlier reports of the association between IEQ/kg with the glycemic control and metabolic outcomes in TP-IAT recipients, these tests lacked utility for predicting the islet yield with great accuracy [47]. At the same time, MMTT, fasting glucose and HbA1c correlated inversely with the final IEQ/kg, that is, patients with impaired fasting and stimulated insulin and C-peptide secretion, as well as HbA1c had fewer islets that could be isolated for transplant.

Patients diagnosed with CP present with various degrees of damage to the pancreatic parenchyma. Those with the most severe pancreatic disease are expected to have lower islet yields as a result of islet isolation in preparation for IAT, mostly due to the underlying damage to the pancreatic tissue and scarring of the pancreas. A small data set obtained from pediatric patients demonstrated that islet yield is compromised when pancreatic fibrosis is severe [48,49]. Considering the fact that the majority of the patients undergoing TP-IAT are adults, Kobayashi *et al.* investigated the relationship between histopathologic injury and islet yield in a large adult patient population [50]. They examined pancreatic histopathology in 105 adult patients who underwent pancreatectomy and AIT; histologic degree of fibrosis, acinar atrophy, inflammation and nesidioblastosis were scored by a surgical pathologist [50]. To avoid biased results, the correlation between islet yields and histologic changes were examined only in those patients who underwent TP and IAT after the introduction of the semi-automated technique for islet isolation [37].

The authors suggested that in patients with intractable CP pancreatectomy should be considered early, before extensive damage to the pancreatic parenchyma and serious risk of diabetes ensues [29]. Fibrosis, acinar atrophy and inflammation of the pancreatic parenchyma demonstrated a negative correlation with the islet yield. There was a positive correlation of islet yield and a negative correlation of fibrosis and acinar atrophy with the islet graft function. In addition, the authors also noted that prior pancreatic surgery – especially surgical drainage by lateral pancreateojejunostomy – for CP had a negative effect on the islet yield at the time of isolation [51]. These results have been confirmed by Hubert *et al.* who found a significant

correlation between an acute insulin response to arginine and glucose and the islet isolation yield in cadaveric donors. Authors suggested donor acute insulin response to arginine is markedly superior to body mass index and other criteria currently used to predict islet yield [52].

MRI is a noninvasive modality that has been demonstrated to correlate with clinical features and the treatment of CP. Khan *et al.* examined whether islet yield can be predicted by MRI preoperative and determined that a diminished islet yield might be predicted on the basis of the delayed interstitial phase magnetic resonance sequence [53]. The authors concluded that noninvasive MRI testing is able to assess the severity of pancreatic damage and CP patients, progression of the disease, and estimated the islet isolation yield [53]. Additionally, clinical image studies such as endoscopic retrograde cholangiopancreatography and EUS have been reported to be associated with the islet yield per patient body weight. This suggests that progression of inflammation leads to worse islet isolation results.

The literature points to the fact that pathological states affecting the integrity of one of the pancreatic compartments can invariably affect the other, due to their close proximity. Impairment of the endocrine function leads to hyperglycemia which affects the exocrine compartment, and eventually, results in pancreatic fibrosis. At the same time, severe impairment of the exocrine tissue (AP or CP) affects the endocrine compartment, increasing the risk of developing glucose intolerance and diabetes. Hence, predictive techniques such as noninvasive imaging and development of various biomarkers predictive of the quality of the endocrine tissue or maybe a combination of both are of paramount importance as a predictor of the disease stage, as well as the quality of the islet cells necessary to reverse the diabetic state after TP. Although imaging studies have been utilized as a predictor of the disease state, and indirectly, of islet cell yield, additional studies are necessary to identify specific markers able to accurately predict the islet isolation outcome. These are critical as the time between TP and islet isolation is limited. Hence, markers that would offer the necessary information in real time would be of great benefit.

#### • Surgical considerations for pancreatic resection

Pancreatic resection, performed to alleviate intractable pain as a consequence of CP, is usually done



by open laparotomy, and is associated with a substantial amount of postoperative pain, wound complications and prolonged recovery period [15]. Despite the fact that minimally invasive surgical approaches offer an opportunity to improve these results, laparoscopic surgery as treatment modality for CP remains one of most challenging applications of minimally invasive surgery. Post-surgical diabetes that ensues following surgery presents an additional complication. Despite these challenges, Giulianotti *et al.* recently reported on the largest series of robotic pancreatic surgeries performed in 124 patients; the authors determined that this type of minimally invasive surgery was both feasible and safe [53]. The authors also described a laparoscopic technique for the resection of the pancreatic head with the preservation of the vascular supply to enable subsequent islet isolation and IAT [54,55]. The surgery was performed using the Da Vinci robotic surgical device, in a 35-year-old woman who presented with intractable chronic pain secondary to CP [54]. The major technical challenge of this procedure was to preserve the vascular supply of the distal pancreas until the last moments of the resection, so that the warm ischemia time to the islets could be kept to a minimum. Generally, to achieve this, the head of the pancreas remains connected to the splenic vessels, that is, splenic artery and vein.

In those cases where head of the pancreas and duodenum are difficult to mobilize, body and tail of the pancreas are removed separately. Accumulated clinical experience clearly demonstrates that duodenal ischemia is common during pancreatic resection [20]. Hence, duodenum sparing technique is utilized whenever possible; in those cases when it is not, an attempt is made to preserve at least the pylorus and the distal section of the duodenum [56]. When preservation of the duodenum is not possible, reconstruction is done using an alternate surgical technique, that is, classic Roux-en-Y choledochojejunostomy and gastro- or duodenojejunostomy [15,42]. Pylorus-sparing pancreatectomy with spared spleen, however, is associated with splenic vein thrombosis and increased risk of left-sided portal hypertension. It results in complications of late gastrointestinal bleeding and painful splenomegaly due to the short gastric varices. Splenomegaly can be extremely painful, so the spleen is spared only when it retains normal appearance following ligation, in approximately 30% of the patients undergoing pancreatectomy. Although

preserving the spleen provides an advantage in terms of fighting infection, no significant differences were found in terms of complications and outcomes between patients who underwent splenectomy and those who did not [57,58].

In the early days of UMN experience with TP-IAT, a considerable effort was made to save the spleen [59]. At present, however, preservation of the spleen is rarely undertaken, to avoid adding unnecessary complications to an already complex surgical intervention.

### Pancreatogenic diabetes

According to the American Diabetes Association and WHO pancreatogenic, pancreoprive or apancreatic diabetes mellitus (DM) is classified as a form (Type 3c) of secondary or Type 3c DM (T3cDM) [60]. AP, CP of any etiology, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, pancreatic trauma leading to loss of pancreatic tissue, pancreatic agenesis, pancreatectomy and pancreatic cancer are the underlying exocrine pancreatic diseases that lead to pancreatogenic diabetes (PD) [61]. These conditions lead to disperse destruction of the pancreas, pancreatic hormone deficiencies and severely altered responses to hormonal stimuli, culminating in impaired glucose metabolism. CP, however, is the most common underlying cause of PD that affects 75–80% of the patients, with pancreatic cancer coming in close second, with 8% of all T3cDM patients affected by this condition [62,63]. A number of different risk factors, such as alcoholism, biliary disease and pancreatic disorders, have been associated with CP. However, the exact etiology of this condition, characterized by pancreatic sclerosis, and endocrine and exocrine insufficiency, remains unknown [59]. That is why the treatment for CP is largely empirical, and includes both clinical and surgical approaches. Severe persistent pain associated with CP and unresponsive to other treatment modalities is often resolved by a surgical solution, that is, near-TP or TP. Both near-TP and TP can ameliorate chronic CP-associated pain. However, a different problem in the form of ‘brittle diabetes’ ensues, and leads to an increased morbidity and mortality in CP patients [15,59,64].

PD after pancreatic resection has a complicated endocrinopathy and a significantly different clinical course compared with Type 1 and Type 2 DM (T2DM). In contrast to T1DM, which is caused by an autoimmune destruction of beta-cells in the pancreas and carries high risk

of hyperglycemia and ketoacidosis, PD is characterized by infrequent ketoacidosis. Compared with T2DM, which is characterized by insulin resistance and relative insulin deficiency, PD patients are sensitive to insulin. Due to increased sensitivity to insulin and reduced glucagon levels, PD patients are prone to frequent hypoglycemic attacks resulting from the administration of exogenous insulin. This condition exacerbated by the deficiency of fat soluble vitamins and mal-digestion of fats and proteins is otherwise known as ‘brittle diabetes’ [62,65–68]. Latrogenic hypoglycemia resulting from an extremely poor diabetes management leads to frequent hospitalizations, serious and irreversible damage to the nervous system, nephropathy, retinopathy and – in some cases – death. Hence, it is imperative to be able to discriminate PD from T1DM and T2DM in order to develop an appropriate and effective long-term therapy [69–71]. To that end, Ewald and Bretzel recommended to use the diagnostic criteria demonstrated in **Box 1** for PD [65].

Despite these criteria, correct diagnosis of T3cDM remains a challenge, with many patients commonly misclassified. However, there are reports of pancreatic polypeptide levels – significantly increased in T2DM patients following nutrient stimuli, while appreciably decreased in T3cDM – utilized as a useful diagnostic tool in T3cDM. Pancreatic polypeptide is produced mainly in the head of the pancreas, and has a critical role in the regulation of insulin receptor and maintaining glucose homeostasis, and hepatic insulin sensitivity [61,65,72].

At the present time no generally established guidelines for the treatment of T3cDM exist [15,73]. Many patients with T3cDM are initially treated with Metformin, as the drug of choice. However, depending on the underlying cause of T3cDM, treatment might be different. For example, in patients with cystic fibrosis insulin therapy

is utilized as a therapy of choice. As the case with T2DM, initial treatment approaches to T3cDM should involve life-style changes – such as weight loss, a diet low in carbohydrates, limited alcohol intake, smoking cessation and physical exercise – along with pancreatic enzyme replacement therapy [15]. As painful complications develop, pancreatic resection to relieve the underlying cause of persistent pain becomes more acceptable.

• **Incidence of pancreatogenic diabetes after pancreatic resection**

The development of PD following various types of pancreatic resection is associated with the type of pancreatic surgery, the progression of the underlying disease and the extent of beta-cell destruction [68].

TP is performed for the multiple conditions that include benign tumors and malignancies requiring surgical intervention, refractory CP, pancreatic fistula and abdominal hemorrhage following pancreatic resection [74]. There is a plethora of literature confirming that TP, as well as pancreatic resection of more than 70% of the pancreas, results in 100% of pancreatogenic diabetes, albeit without an inflammation of the pancreatic parenchyma [65,67,73]. It is the severe deficiency in pancreatic hormones following TP that leads to the extreme symptoms of PD [67]. Jethwa *et al.* compared glycemic control in patients with PD and after TP to T1DM; they demonstrate that diabetes control following TP is not necessarily associated with poor glycemic control, relative to T1DM [75]. Although quality control in majority of such patients improves following pancreatic resection, hypoglycemia-associated mortality, and morbidity as a result of nephropathy, retinopathy and neuropathy should be taken into account [74–76].

Distal pancreatectomy is the resection of the tail and body of the pancreas, where the resection

**Box 1. Diagnostic criteria for pancreatogenic diabetes.**

**Proposed major criteria (all must be fulfilled)**

- Presence of exocrine pancreatic insufficiency (according to the monoclonal fecal elastase 1 test or direct function tests)
- Pathological pancreatic imaging (endoscopic ultrasonography, MRI and computed tomography)
- Absence of Type 1 diabetes-associated autoimmune markers

**Minor criteria**

- Impaired β-cell function (e.g., HOMA-B and C-peptide:glucose ratio)
- No excessive insulin resistance (e.g., HOMA-IR)
- Impaired secretion of incretins (e.g., GLP-1)
- Low serum levels of lipid-soluble vitamins (e.g., vitamins A, D, E and K)

volume depends on the extent of the underlying disease. Studies of the patients that underwent distal pancreatectomy as a treatment for CP demonstrate that 25–50% of such patients are at risk of developing PD shortly after surgery [77]. In the prospective study of 500 CP patients, Malka *et al.* tried to elucidate the risk factors associated with the onset of PD [71]. The authors compared patients who underwent elective pancreatic surgery with those without any surgery. The study reported that at 25 years following the onset of CP the prevalence of PD did not increase in the surgical group of patients compared with the nonsurgical group, with the cumulative risk of developing diabetes of 83% [71]. At the same time, distal pancreatectomy did impact glucose metabolism and/or fasting glucose in a significant fashion. Hence, the development of late-onset PD should be monitored in such patients.

Pancreatic resection as a result of pancreatic tumors was found to have an even lesser impact on endocrine function compared with resection due to CP [67,78]. It has been demonstrated that the rate of new onset DM in nondiabetic patients undergoing distal pancreatectomy for pancreatic neoplastic lesions is approximately 5–10% [67].

Central pancreatectomy is the resection of the body segment of the pancreatic parenchyma, and is utilized mostly for patients with benign tumors located in the body of the pancreas. Although this type of procedure results in significant beta-cell loss and impaired glucose metabolism, few patients develop DM, which indicates long-term preservation of endocrine function.

Proximal pancreatic resection is the resection of the head of the pancreas. The rate of newly diagnosed diabetic patients following this procedure has been reported in the literature as 4–17% of patients within 2 years after surgery [67]. This ratio increases to 9–50% during extended follow-up. Forty three (43%) percent of healthy patients undergoing hemipancreatectomy for the purpose of pancreas donation between 1997 and 2003 have demonstrated impaired fasting glucose, impaired glucose tolerance, or diabetes on extended follow-up [78]. Kendall *et al.* confirmed these results, by reporting a significant deterioration of insulin secretion and glucose tolerance 1 year after hemipancreatectomy in healthy donors [70].

#### • Treatment

As discussed in the previous section, despite the attempts to avoid PD following pancreatic

resection, most cases require some form of surgical intervention especially for the treatment of pancreatic tumors or complicated cases of CP. In many cases, pancreatectomy causes insulin-dependent PD which, sometimes, leads to poor metabolic control. However, as discussed previously, patients with TP fair quite well in terms of metabolic and glycemic control, when compared with patients with T1DM [75].

When DM is mild, changes of lifestyle such as exercise, diet modifications and oral anti-diabetic drugs are effective. In advanced PD, insulin replacement therapy is commenced, and is administered according to the insulin regimen and dosing guidelines recommended for patients with T2DM [69]. However, exogenous insulin therapy results in frequent hypoglycemic episodes due to the reduced glucagon levels, increased peripheral sensitivity to insulin, altered intestinal absorption and exocrine deficiency [67]. In an effort to reduce the incidence of hypoglycemic episodes, pancreatic enzyme replacement therapy has been suggested as an effective strategy to restore glycemic control. In fact, it has been demonstrated that the correct dose of pancreatic enzymes in patients with PD can restore glycemic control, prevent nutritional and metabolic complications, and control insulin sensitivity and hyperinsulinemia [79,80].

#### Conclusion & future perspective

Although treatment for CP is largely empirical, several treatment modalities have been developed. However, approximately 50% of the patients with CP experience severe recurring pain refractory to medical intervention. These patients are forced to consider surgical approaches such as near-TP or TP, which often result in alleviation of pain. However, near-TP and TP result in PD which is often difficult to manage, and associated with postoperative morbidity and mortality. IAT after near-TP or TP is performed as the prophylaxis for iatrogenic diabetes which often develops following pancreatic resection, near-TP or TP. IAT after TP has been demonstrated to successfully prevent or minimize PD by preserving beta-cell mass and insulin secretory capacity [4,41,81]. A number of studies indicate that following IAT as a prophylaxis for TP many patients remain insulin-independent for years following transplant [4,41,81].

As discussed above, severe impairment of the exocrine compartment of the pancreas as a consequence of AP or CP results in a severe

endocrine tissue deficiency, glucose intolerance and diabetes, before and/or after near-TP or TP. Hence, the pathology of the exocrine compartment affects the integrity of the endocrine tissue. Hence, in patients for whom IAT is a recommended option, the degree of the exocrine insufficiency can greatly affect the quality and quantity of the islet cells. Imaging studies and biomarkers that can accurately predict the islet cell yield and function would be of benefit. The development of such markers could extend the utility of IAT after TP to patients with more severe and/or advanced pancreatic disease. With longer life expectancy, the number of patients undergoing TP is growing. Given better assessment tools prior to TP, this type of treatment

modality can be expanded to a larger numbers of patients.

The merits of IAT following near-TP or TP will be discussed in detail in chapter II of this manuscript [1].

### Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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