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Glycemic Outcomes of Islet Autotransplantation

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Abstract

Purpose of Review While there has been a growing utilization of total pancreatectomy with islet autotransplantation (TPIAT) for patients with medically refractory chronic pancreatitis over the past few decades, there remains a lack of consensus clinical guidelines to inform the counseling and management of patients undergoing TPIAT. In this article, we review the current clinical practice and published experience of several TPIAT centers, outline key aspects in managing patients undergoing TPIAT, and discuss the glycemic outcomes of this procedure.

Recent Findings Aiming for lower inpatient glucose targets immediately after surgery (usually 100–120 mg/dl), maintaining all patients on subcutaneous insulin for at least 3 months to "rest" islets before an attempt is made to wean insulin, and close outpatient endocrinology follow-up after TPIAT particularly in the first year is common and related to better outcomes. Although TPIAT procedures and glycemic outcomes may differ across surgical centers, overall, approximately one third of patients are insulin independent at 1 year after TPIAT. Higher islet yield and lower preoperative glucose levels are among the strongest predictors of short-term post-operative insulin independence. Beyond 1 year post-operatively, the clinical management and long-term glycemic outcomes of patients after TPIAT are more variable.

Summary A multidisciplinary approach is essential in optimizing the preoperative, inpatient, and post-operative management and counseling of patients about the expected glycemic outcomes after surgery. Consensus guidelines for the clinical management of diabetes after TPIAT and harmonization of data collection protocols among TPIAT centers are needed to address the current knowledge gaps in clinical care and research and to optimize glycemic outcomes after TPIAT.

Keywords Total pancreatectomy with islet autotransplantation · Islet autotransplantation · Insulin independence · Glycemic outcomes

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Introduction

Total pancreatectomy is a surgical procedure that can relieve medically refractory pain in patients with chronic pancreatitis (CP). Total pancreatectomy, however, inevitably renders these patients with post-surgical diabetes. While post-pancreatectomy diabetes is similar to type 1 diabetes as a condition of absolute insulin deficiency, the etiology is different. Additionally, the surgical removal of alpha cells in the pancreas also abolishes the glucagon counterregulatory response to hypoglycemia, such that glycemic management becomes more challenging in patients after total pancreatectomy. In an effort to preserve beta-cell function and maintain endogenous insulin production after total pancreatectomy for medically refractory CP, the world's first case of total pancreatectomy with islet autotransplantation (TPIAT) was performed in

1977 [1]. Since that time, there has been a growing interest in TPIAT and an expansion in the number of centers offering this procedure in the USA and around the world. Nowadays, endocrinologists and other diabetes care providers are more likely to encounter patients who have undergone, or are considering, TPIAT than before. In this article, we outline the key aspects of the surgical procedure, patient selection, and indications of TPIAT. We also review the multidisciplinary approach and current clinical practice in managing patients before, during, and after the surgery and discuss the reported glycemic outcomes after TPIAT.

Surgical Procedure and Patient Selection

Removal of Pancreas

In most centers, total pancreatectomy is performed via an open procedure, but some programs now offer laparoscopic approaches [2, 3]. During the procedure, blood supply is maintained until the entirety of the gland is mobilized. When there is difficulty mobilizing the head, as in the case of some laparoscopic procedures, the head and body/tail of the pancreas can be removed separately, maintaining blood supply to each section of the pancreas until complete removal of the gland. These measures are designed to reduce ischemic time [2, 3]. In many centers, patients undergo resection of the spleen and much of the duodenum with reconstruction. More recently, a few reports of robotic-assisted TPIAT have been published with favorable short-term safety data and the potential for faster recovery time and lower post-operative morbidity [4].

Islet Digestion, Isolation, and Infusion

Islet digestion and isolation generally occurs through a method similar to that originally described by Ricordi et al. [5] After removal of the pancreas, which can occur in sections, a mix of collagenase and protease is injected into the pancreatic ductal system to begin gland digestion [2, 6, 7]. Pancreatic tissue is then placed in a digestion chamber (commonly a Ricordi Islet Isolator [5]) and processed at temperatures around 37 °C. Upon satisfactory digestion, the introduction of cold medium halts the digestion process [8]. Islets are resuspended in 2.5–20% human serum albumin, varying by institution, for transplantation [2, 3, 6]. A heparin infusion often precedes the islet infusion or is part of the islet suspension, to reduce the risk of thrombosis. Most programs transfuse islets into the liver commonly via the portal vein or sometimes a colic vein [2, 6, 8–13]. However, other sites of transfusion include the spleen [14] and muscles of the forearm [15], though these are not yet used commonly. Monitoring of portal venous pressures is common during the infusion process, especially when larger islet yields are obtained [2, 3, 6, 10, 16].

Islet processing often occurs on-site, either on the same day of surgery or on a different day. However, centers that do not have the ability to isolate islets on-site can send the surgically removed pancreatic tissue off-site to another facility for processing. When the islet processing occurs at another facility, or at the same facility but on a different day, the patients are typically closed and sent to a post-anesthesia unit until the islets are infused [11, 16]. Nonetheless, the islet yields and insulin independence seem to be comparable between centers that perform on-site versus off-site islet processing [9]. The volume of the transplanted pancreas must be considered, as larger volumes have been associated with portal vein thrombosis and liver damage. Thus, some centers employ a process of "islet purification" to minimize the volume of the infusion while preserving the islet numbers. Most current purification methods employ a density-dependent separation, as islets have a lower density than exocrine pancreas tissue. The COBE 2991 cell processor is commonly used for islet purification, when required [7]. However, as this process requires extra time, many centers may not necessarily perform this extra step or only perform it with higher tissue volumes [2, 8, 16, 17].

Islet size varies substantially throughout the normal pancreas, with diameters ranging from 50 to greater than 350 μm [7]. In an effort to standardize the yield of transplanted tissue, the 2nd Congress on International Pancreas and Islet Transplantation Association reached a consensus on criteria for measuring the quantity of islets, standardizing an "islet equivalent" or "IE" as 150 μm [18]. To obtain an estimate of total islets transplanted, a sample of the resuspended islet preparation is stained with dithizone and counts are performed, converting to IEs [6, 17]. These counts can either be performed manually or with automated counters with some differences in precision [3]. Overestimation of islet count is more common when islet yield is obtained from automatic versus manual counting.

Potential Complications

Transplantation-specific complications from TPIAT generally include portal vein thrombosis and liver damage. General surgical complications from the pancreatectomy can include bleeding (reported to be higher if post-infusion portal pressures were elevated) [2], infection, anastomatic leaks, bowel obstruction, omental infarction, bowel perforation, delayed gastric emptying, or pancreatic bed fluid collection [2, 8, 10, 16]. A retrospective study comparing TPIAT to total pancreatectomy alone found that the rates of major morbidity and transfusion were higher in the TPIAT group and that group also had a longer length of stay compared to the total pancreatectomy alone group (13 days versus 9 days, respectively). However, there was no difference in mortality between the two groups [19]. Finally, symptoms of gastrointestinal

dysmotility have been reported in up to half of patients who have undergone TPIAT [20].

Indications and Timing of TPIAT

Indications for TPIAT vary by institution due to the lack of standardized patient selection protocols; but in general, for the indication of CP, patients must have proven CP with sustained (usually > 6 months) pain that interferes with their daily activities and which fails maximal medical interventions [2, 21, 22••]. Many patients with "idiopathic" CP are screened preoperatively for genetic causes, such as the loss of function mutations of pancreatic secretory trypsin inhibitor (SPINK1), cationic trypsinogen (PRSS1), cystic fibrosis trans-membrane conductance regulator (CFTR), chymotrypsinogen C (CTRC), and several others [23, 24]. Some institutions will perform TPIAT for pancreatitis for patients who have a genetic mutation that also increases the risk of development of pancreatic cancer (such as PRSS1) even if pain symptoms are not yet severe, or CP in the absence of main duct pathology [3, 12, 25, 26]. Less commonly, some centers may perform TPIAT for relapsing acute pancreatitis [25], those at high risk for leakage after pancreaticoduodenectomy or those with complications after pancreatic surgery [27]. For the autotransplantation portion of the procedure, while patients must at a minimum be C-peptide positive preoperatively, many centers offer TPIAT to patients with prediabetes or diabetes diagnoses, including those treated with insulin, as long as there is endogenous islet function [9, 28••]. Exclusion criteria generally include cirrhosis, active alcohol/drug use, and psychiatric illness with inability to adhere to medical instructions [2, 9]. Individuals with pancreatic cancer or a suspicious pancreatic mass are generally excluded, though few centers have reported performing TPIAT when a benign pancreatic lesion is present [21, 27, 29, 30]. Some institutions will perform TPIAT on the residual pancreatic tissue after surgery for pancreatic carcinoma; however, this is not a commonly accepted procedure in the USA. [30–32]

Clinical Management

Multidisciplinary Team Management

Over the past few decades, the patient selection criteria have evolved and the approach to determining the appropriate candidates and managing patients after TPIAT has transitioned to a multidisciplinary team approach. Though members of the multidisciplinary teams vary among the less than a dozen academic hospital centers currently offering TPIAT in the USA, they usually all include at least a pancreatic surgeon, endocrinologist, and gastroenterologist. Some other possible members include clinical nurse specialist, nurse practitioner, pain management specialist, anesthetist, medical psychologist, radiologist, islet biologist, and dietician [33].

Pre-surgical Assessment of Patients

Demographic, clinical, health-related quality of life outcomes (QOL), pain assessments, and operative data are often collected on patients. Endocrinologists evaluate endogenous islet function with at a minimum the preoperative hemoglobin A1C, C-peptide, and fasting glucose usually obtained. In some centers, a 75-g oral glucose tolerance test (OGTT) with glucose, insulin, and C-peptide measured at 0, 1, and 2 h [28••]; mixed meal tolerance test (MMTT) [34], C-peptide along with fat soluble vitamins (ADEK); and/or lipids are also assessed.

Post-surgical Management of Patients

Inpatient Management Intravenous insulin drip is initiated at the same time the pancreas is resected to maintain tight glucose control usually between 100 and 120 mg/dl [2, 28••]. After 72 h post-operatively, patients are usually transitioned to subcutaneous basal insulin therapy with additional prandial and correctional insulin added as needed (Fig. 1). Diabetes education is given and insulin doses are adjusted as necessary to achieve glucose goals similar to other patients with diabetes. All patients are discharged on subcutaneous insulin regimens including basal and/or bolus insulin for at least 3 months unless prevented by recurrent hypoglycemia [28••].

Post-discharge Outpatient Management There is consensus that subcutaneous insulin therapy should be continued for at least 3 months to "rest" the transplanted islets and minimize any beta-cell stress from hyperglycemia. In general, attempts are made to wean patients off insulin at 3 months as long as blood glucose levels are near target range [i.e., fasting < 130 mg/dl, post prandial < 180 mg/dl, and/or hemoglobin A1C of 6.5% (48 mmol/mol) or less]. The target hemoglobin A1C level of 6.5% (48 mmol/mol) is optimal to minimize hyperglycemic stress of the islets [2]. Patients are seen at different frequencies post operatively but most consistently at 3 months, 6 months, 1 year, and then ideally at least annually or more frequently depending on whether they have diabetes. Assessment of islet graft function and glycemic control are done by regularly monitoring fasting C-peptide, fasting glucose (and perhaps also fasting insulin), hemoglobin A1C, and in some cases OGTT and MMTT evaluations. Differential kinetics of glucose absorption among patients with chronic pancreatititis due to exocrine insufficiency or with previous surgical removal of the duodenum (i.e., Whipple) is yet to be determined and could be a potential limitation of the use of OGTT and MMTT in this setting.

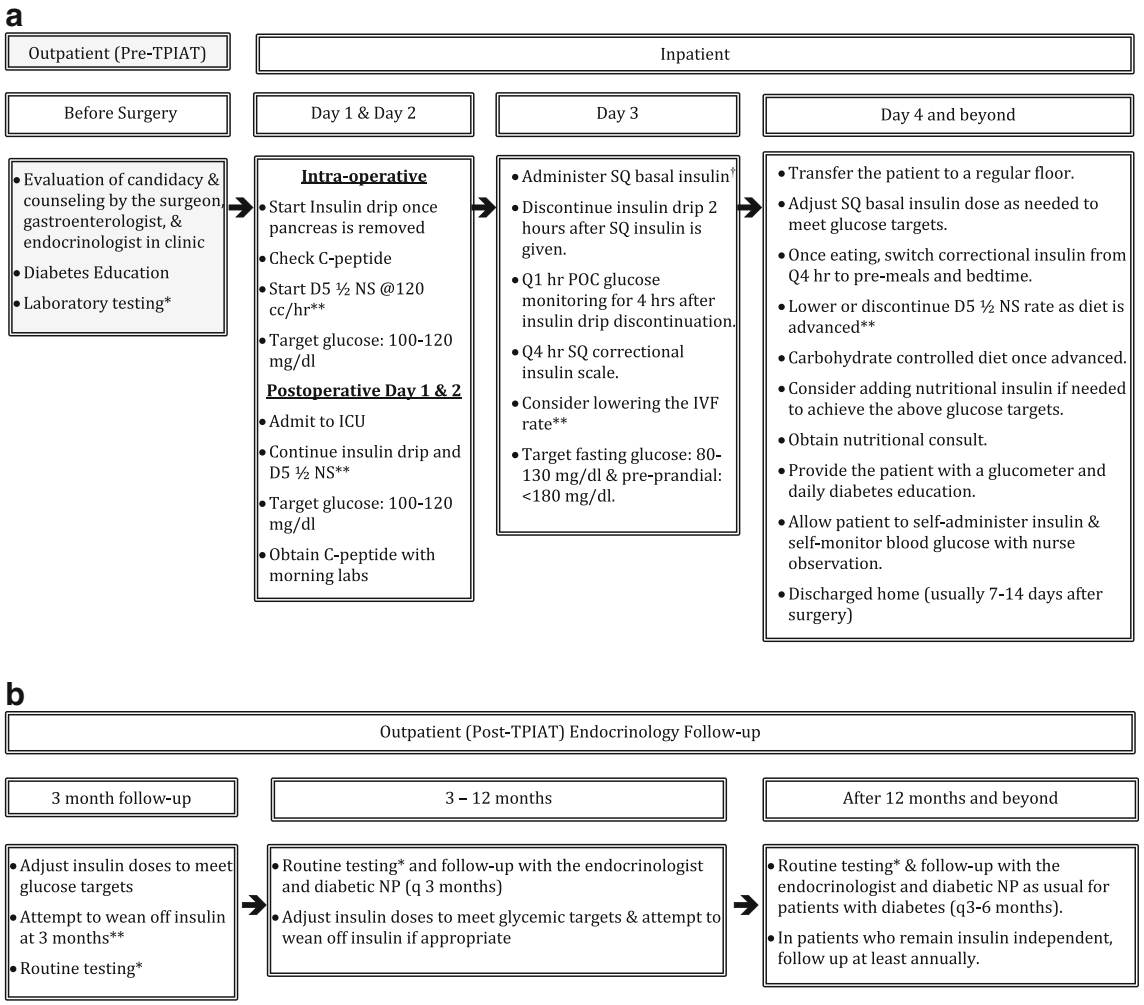

Fig. 1 a A flow chart of the suggested preoperative and inpatient clinical care of patients undergoing TPIAT. An asterisk indicates routine laboratory testing which includes A1C and fasting glucose, insulin, and C-peptide. Some centers perform 75 g OGTT in those without diabetes at interval clinic visits or mixed meal tests. Double asterisks indicate that rate and type of dextrose containing fluid should be adjusted based on the patient's underlying comorbidities and volume status. A dagger indicates that basal insulin dose is to be decided by the managing provider. SQ subcutaneous, hr hour, POC point of care, IVF intravenous fluid, NP nurse practitioner. **b A flow chart of the suggested post-operative outpatient clinical care of patients undergoing TPIAT**. An asterisk indicates routine laboratory testing which includes A1C and fasting glucose, insulin, and C-peptide. Some centers perform 75 g OGTT in those without diabetes at interval clinic visits or mixed meal tests. Double asterisks indicate that usually, weaning off insulin is attempted if the patient is requiring less than 10 to 20 units a day to maintain target glucose levels. SQ subcutaneous, hr hour, POC point of care, IVF intravenous fluid, NP nurse practitioner

Glycemic Outcomes after TPIAT

While the primary goal of TPIAT is to relieve medically intractable pain from chronic pancreatitis, another important goal is to maintain euglycemia and insulin independence in those who did not have diabetes before surgery and sustain as much residual endogenous insulin secretion as possible in those who had diabetes to reduce the post-operative insulin requirement. Data on short- and long-term glycemic outcomes and insulin independence after TPIAT are now available from several centers. However, there is lack of detailed reporting of the glycemic outcomes in some of the studies and considerable variability in duration of follow-up and definitions used to refer to insulin independence. In general, insulin independence is defined as not requiring any insulin therapy to maintain glucose levels at target ranges [fasting < 130 mg/dl, postprandial < 180 mg/dl, and hemoglobin A1C < 6.5% (48 mmol/mol)] [2]. Attempts to wean from subcutaneous insulin typically begin no sooner than 3 months after TPIAT. Individuals who continue to require a basal-bolus insulin regimen to maintain glucose levels within target ranges are referred to as insulin dependent [2]. C-peptide level has also been included in the definition of insulin independence in some studies, and various C-peptide cutoff levels have been used to indicate graft failure. For example, the International Transplant Registry suggests using a fasting C-peptide level of < 0.3 ng/mL to indicate graft failure, but a higher C-peptide cutoff (e.g., < 0.6 ng/mL) has also been used in literature [2,

35]. It is thought that a C-peptide cutoff of 0.6 ng/mL is more clinically relevant and may correlate better with glycemic outcomes, though the evidence for this is based on extrapolation from the Diabetes Control and Complications Trial and other studies in patients with type 1 diabetes [36]. Partial graft function is another term used in literature to refer to individuals with C-peptide ≥ 0.6 ng/mL who are able to maintain target glucose levels on basal insulin (± as needed short-acting correctional insulin) [2]. Others define partial graft function as requiring fewer than 20 units of insulin per day after TPIAT [25]. Over time, it is not uncommon for insulin-independent patients to become insulin dependent. To address the lack of consistent definitions of beta-cell function and failure after islet transplants, the International Pancreas & Islet Transplant Association and the European Pancreas and Islet Transplant Association proposed a four-tiered system to classify the functional outcomes of islet transplants. This classification system has the potential to be adopted and used in patients undergoing TPIAT to standardize the glycemic outcome reporting across the TPIAT centers [37, 38].

Short-term Glycemic Outcomes (the First Year Post-TPIAT)

The islet grafts appear to function optimally up to 1 year after TPIAT with insulin requirement being the lowest at that time in the Leicester series [14]. Rates of insulin independence were also found to be the highest around 1 year after TPIAT in a meta-analysis of 12 TPIAT studies [39••]. Ten of the 34 (29%) patients who underwent TPIAT at our center at Johns Hopkins Hospital between 2011 and 2016 were insulin independent at 1 year after TPIAT; a rate that is similar to those reported by other TPIAT centers (between 28 and 38%) [2, 25, 28••]. However, among these patients, post-operative insulin independence can be a transient phase that lasts for an average of 17.7 months [95% CI 10.91–24.52]. Transient insulin independence after TPIAT has been reported to occur in approximately 7 cases per 100 person-years [39••].

Long-term Glycemic Outcomes (after the First Year Post-TPIAT)

One of the earliest reports of long-term glycemic outcomes after TPIAT in 2001 showed that 5 out of 6 patients who underwent TPIAT remained insulin independent after 3 to 13 years of follow-up [40]. More recent data has been published from several centers around the world. In 2012, the Minnesota group reported their experience with 409 patients who underwent TPIAT between 1977 and 2011. The proportion who were insulin independent remained stable between 1 and 3 years after TPIAT (28% versus 30%, respectively) [2]. Patients who were insulin independent at 2 years after TPIAT were very likely to remain insulin independent afterward. Among those on insulin treatment, the proportion of patients with partial graft function (defined in this series as having either C-peptide ≥ 0.6 ng/mL or euglycemia while taking once-daily basal insulin), declined significantly from 49% at 1 year to 33% at 3 years. Many of these patients with partial graft function progressed to become insulin dependent (defined as having C-peptide < 0.6 ng/mL or using basal-bolus insulin regimen to maintain euglycemia) between 1 and 3 years after TPIAT [2]. More recently, the Cincinnati group reported the long-term outcomes of 112 patients who underwent TPIAT between 2000 and 2013 and had at least 5-year follow-up data [25]. The percentage of patients who were insulin independent in this series was 38% at 1 year and 27% at 5 years or more. The proportion of patients with partial graft function (defined in this series as those requiring less than 20 units of insulin a day) slightly declined from 38% at 1 year to 35% at 5 years. Data from the Leicester General Hospital showed that 12 out of 46 patients who underwent TPIAT had a period of insulin independence that lasted anywhere between 2 and 63 months. [14] Interestingly, long-term endogenous insulin secretion, as demonstrated by detectable C-peptide, appeared to be maintained over the 10 years of follow-up in all patients at this center, albeit reduced levels compared to immediately after surgery [14].

Predictors of Insulin Independence after TPIAT

Identification of preoperative predictors of insulin independence can help identify TPIAT candidates who are more likely to remain insulin independent after surgery, and facilitate the appropriate preoperative counseling for all patients regarding their expected glycemic outcome after TPIAT. In this section, we will review some preoperative and perioperative factors that have been described in the literature as potential predictors of post-surgical insulin independence following TPIAT.

Islet Yield Islet yield refers to the number of islets isolated from surgically excised pancreatic tissue and available for autotransplantation, which can be counted manually or using an automatic counter. Many reports have suggested a positive association between islet yield and the likelihood of insulin independence post-TPIAT and this is the most consistent perioperative predictor described in literature [2, 9, 21, 26, 41]. However, islet yield alone does not appear to be sufficient in predicting insulin independence in all studies. For example, in one series, insulin independence at 2 years post-TPIAT was still achieved in up to 15% of those with the lowest islet yield (i.e., < 2500 islets equivalents per recipient body weight (IEQ/kg)) [2]. Not all TPIAT series have reported the same association between islet yield and insulin independence [28••], raising the question of whether variability in islet graft survival after transplantation could potentially explain the

inconsistency seen in these results, limiting the prognostic significance of using islet yield alone as a predictor of insulin independence. Importantly, information about islet yield cannot be determined until the time of surgery and is generally difficult to predict preoperatively. Preoperative glycemic measures such as glucose, insulin, and C-peptide are inconsistently related to islet yield [25, 28••, 34]. Greater pancreatic fibrosis and prior pancreatic surgeries have both been associated with lower islet yield [13, 42]. In general, the likelihood of insulin independence after TPIAT is higher in those without diabetes before surgery, especially when the islet yield is greater than 5000 IEQ/kg (or 500,000 IEQ) [2]. To put this in perspective, the normal adult pancreas consists of approximately 1 million islets distributed throughout the pancreas [43].

Preoperative Glycemic Measures We have previously reported a significant relationship of several preoperative glycemic measures to insulin independence after TPIAT at Johns Hopkins Hospital [28••] In our series of 34 patients who underwent TPIAT and had preoperative OGTT performed, lower preoperative fasting and 1-h and 2-h glucose levels were all strong predictors of insulin independence at 1 year after TPIAT. In addition, preoperative HOMA-B was the strongest predictor of insulin independence. Interestingly, all patients who had prediabetes preoperatively (defined as impaired fasting glucose and/or impaired glucose tolerance) were insulin dependent 1 year after TPIAT. It is also worth noting that one third of the prediabetes cases in our series were identified solely based on the presence of impaired glucose tolerance, and therefore would have been missed without preoperative OGTT [28••]. This supports the potential utility of OGTT in pre-surgical evaluation of TPIAT candidates. Others have shown that higher preoperative C-peptide in individuals with diabetes undergoing TPIAT is associated with greater likelihood of having detectable C-peptide (≥ 0.6 ng/mL) after TPIAT, which protects against the development of "labile" post-pancreatectomy diabetes that is typically challenging to manage [36]. In addition, the insulin and C-peptide responses to intravenous arginine have been shown to correlate very highly with the number of islets transplanted in TPIAT recipients and may serve as a reasonable surrogate measure of islet mass, survival, and function post-TPIAT [40, 44]. A better glycemic status in the first few days post-operatively has also been linked to higher likelihood of long-term insulin independence [9].

BMI The relationship between obesity and insulin resistance is well established and it is not surprising that patients with higher BMI undergoing TPIAT are more likely to be insulin dependent after the procedure. This was shown by Ahmad et al., where patients with BMI greater than 28 kg/m^2 (or an absolute weight of 78 kg) had a higher risk of being insulin dependent within 5 years after TPIAT [41]. However, this association between high BMI and risk of insulin dependence has not been consistently shown in the few studies that monitored patients for more than 5 years after TPIAT but may be due to the small number of cases with reported outcomes beyond 5 years from TPIAT [14, 25]. Whether non-alcoholic fatty liver disease/non-alcoholic steatohepatitis seen with obesity could negatively impact the survival and function of the intrahepatic islet graft is a potential area of research. In general, it is commonly recommended that patients with very high BMI lose weight before TPIAT.

Sex Women were more likely to be insulin independent after TPIAT in some TPIAT series for reasons that are unknown [9, 25, 28••]. It is postulated that differences in hormonal milieu in the liver or possibly the lower pain threshold generally found in women, prompting them to seek medical attention sooner than men, may contribute to the sex discrepancy in insulin independence rates after TPIAT. Further research is needed to explore the potential mediators of insulin independence after TPIAT in women.

Quality of Life

Patients with chronic pancreatitis suffer from debilitating pain that usually results in impaired quality of life, depression, frequent emergency department visits and hospitalizations, and inability to attend work or school [45, 46]. The primary goal of TPIAT is to relieve pain which can help restore QOL. Both severity of pain and quality of life have been shown to significantly improve after TPIAT in many centers [2, 47–49]. QOL as measured by Short Form (SF-36) improves regardless of insulin independence status, though those who remain insulin independent seem to have greater improvement in all dimensions of the SF-36 survey compared to those who do not. [2] This indicates the important role of preserving islet cell function not only on improving glycemic outcomes but QOL as well.

Limitations and Future Directions

Although there has been an increasing utilization of TPIAT over the past four decades, many questions remain about the appropriate candidates, optimal time to operate, and predictors of glycemic and QOL outcomes. There is a need to standardize clinical measurement protocols and develop uniform practice guidelines on how to assess patients before TPIAT and monitor them perioperatively and after surgery. The Prospective Observations Study of TPIAT (POST) is the first large multicenter study of TPIAT and is currently enrolling subjects from nine centers in the USA [50]. The aim of

POST is to examine patient and disease characteristics that are associated with improvement in pain, QOL, and glycemic outcomes and serve as an initiative toward standardizing clinical care and outcome reporting in TPIAT centers. Future research should focus on optimizing glycemic outcomes for patients after TPIAT, and improving islet isolation and engraftment techniques, in addition to developing new biomarkers and imaging tools that can monitor the function and location of the islet cells and assess their viability after transplantation.

Conclusions

There has been an increasing utilization of TPIAT for the management of medically refractory chronic pancreatitis since the 1970s. Yet, many questions about the appropriate candidates, surgical techniques and tools, patient counseling, glycemic outcomes, and diabetes management of patients after TPIAT remain to be answered. The most consistently reported predictor of insulin independence after TPIAT is islet yield; however, this cannot be determined before surgery. There is a growing literature reporting the utility of measuring various preoperative glycemic markers, to predict insulin independence. The ability to better predict glycemic outcomes of TPIAT in the future can ultimately help providers more appropriately manage and counsel patients and add another dimension to the preoperative discussion regarding "risks and benefits" of TPIAT. There are currently no consensus clinical practice guidelines on how to counsel and manage patients who are undergoing TPIAT, and the bulk of diabetes management for these patients currently occurs in the academic centers that have experience with the surgery. As popularity for TPIAT continues to grow, more health care providers will need to become familiar with how to optimize glycemic outcomes and manage diabetes in this unique patient population. The development of such standardized preoperative assessment protocols and multicenter collaboration is needed in the future to ensure optimal glycemic and QOL outcomes and help addressing the current knowledge and research gaps.

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Compliance with Ethical Standards

Conflict of Interest Mohammed E. Al-Sofiani, Michael Quartuccio, Erica Hall, and Rita R. Kalyani 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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