Langenbecks Arch Surg (2017) 402:873–883
DOI 10.1007/s00423-017-1603-8

REVIEW ARTICLE

Perioperative management of endocrine insufficiency after total pancreatectomy for neoplasia

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Received: 15 January 2017 / Accepted: 7 July 2017 / Published online: 21 July 2017

Abstract
Purpose Indications for total pancreatectomy (TP) have increased, including for diffuse main duct intrapapillary mucinous neoplasms of the pancreas and malignancy; therefore, the need persists for surgeons to develop appropriate endocrine post-operative management strategies. The brittle diabetes after TP differs from type 1/2 diabetes in that patients have absolute deficiency of insulin and functional glucagon. This makes glucose management challenging, complicates recovery, and predisposes to hospital readmissions. This article aims to define the disease, describe the cause for its occurrence, review the anatomy of the endocrine pancreas, and explain how this condition differs from diabetes mellitus in the setting of post-operative management. The morbidity and mortality of post-TP endocrine insufficiency and practical treatment strategies are systematically reviewed from the literature. Finally, an evidence-based treatment algorithm is created for the practicing pancreatic surgeon and their care team of endocrinologists to aid in managing these complex patients.
Methods A PubMed, Science Citation Index/Social sciences Citation Index, and Cochrane Evidence-Based Medicine database search was undertaken along with extensive backward search of the references of published articles to identify studies evaluating endocrine morbidity and treatment after TP and to establish an evidence-based treatment strategy.
Results Indications for TP and the etiology of pancreatogenic diabetes are reviewed. After TP, ~80% patients develop hypoglycemic episodes and 40% experience severe hypoglycemia, resulting in 0–8% mortality and 25–45% morbidity. Referral to a nutritionist and endocrinologist for patient education before surgery followed by surgical reevaluation to determine if the patient has the appropriate understanding, support, and resources preoperatively has significantly reduced morbidity and mortality. The use of modern recombinant long-acting insulin analogues, continuous subcutaneous insulin infusion, and glucagon rescue therapy has greatly improved management in the modern era and constitute the current standard of care. A simple immediate post-operative algorithm was constructed.
Conclusion Successful perioperative surgical management of total pancreatectomy and resulting pancreatogenic diabetes is critical to achieve acceptable post-operative outcomes, and we review the pertinent literature and provide a simple, evidence-based algorithm for immediate post-resection glycemic control.

Keywords Total pancreatectomy · Endocrine insufficiency · Pancreatogenic diabetes · IPMN · Management

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Introduction

Clinical indications for total pancreatectomy (TP) have expanded over recent years. Though the radicality of resection for many pancreatic tumors has decreased, there has been an extension of resection criteria for pancreatic malignancies and metastatic disease, in addition to a greater understanding of the natural history of premalignant neoplasms, including diffuse main duct intraductal mucinous neoplasms of the pancreas (IPMN) [1–5].

The brittle diabetes that results from total pancreatectomy is a source of significant morbidity and mortality and a leading cause of post-operative hospital readmissions. The estimated healthcare cost of a patient with brittle diabetes in the USA is $1500 per year compared with $564 per year for patients with non-pancreatogenic diabetes [6]. These are likely underestimated figures, though the proportional cost increase of brittle diabetes over type 1 or 2 diabetes highlights that these patients consume both increased time and healthcare resources. We found a need for a standardized, simple, and easy to follow algorithm to manage patient blood glucose after TP. This article aims to define the disease, describe the cause for its occurrence, review the anatomy of the endocrine pancreas, and explain how this condition differs from diabetes mellitus in the setting of post-operative management. The morbidity and mortality of post-TP endocrine insufficiency and practical treatment strategies are systematically reviewed from the literature. Finally, an evidence-based treatment algorithm is created for the practicing pancreatic surgeon and their care team of endocrinologists to aid in managing these complex patients.

Materials and methods

A systematic review was performed, in accordance with the PRISMA (*p*referred *r*eporting *i*tems for *s*ystematic reviews and *m*eta-*a*nalyses) statement, to identify articles published that addressed post-pancreatectomy diabetes. An electronic literature search was performed of all publications from January 1, 1997 to January 1, 2017 to identify published data on pancreatogenic diabetes after total pancreatectomy. Databases searched were PubMed, Science Citation Index/Social sciences Citation Index, and Cochrane Evidence-Based Medicine. Terms used in the search were "total AND pancreatectomy AND diabetes." The search strategy within PubMed was further enhanced to retrieve citations identified as systematic reviews, meta-analyses, reviews of clinical trials, evidence-based medicine, consensus development conferences, guidelines, and citations to articles from journals specializing in review studies of value to clinicians to identify all articles related to this topic that address the endocrine morbidity of TP and treatment strategies. Backward search of the references of published articles to identify studies evaluating endocrine morbidity and treatment after TP and to establish an evidence-based treatment strategy were added. Studies were included if they described physiological function of the pancreas, brittle diabetes following pancreatectomy, morbidity, and mortality of post-pancreatectomy diabetes or management of post-pancreatectomy diabetes. All series satisfying these criteria were included regardless of the size of the study population. Case reports, editorials, and unpublished data from conference abstracts were excluded. The initial search identified 588 articles. Applying the filters described resulted in the exclusion of 254 articles.

Results

Definition and causes of brittle diabetes

In the 1930s, Chicago physician R.T. Woodyatt introduced the concept of *brittle* diabetes as excessive fluctuations of blood sugar that could not be explained by the patient or by physician errors [7, 8]. Endocrine insufficiency secondary to TP can result in wide, fast, unpredictable, and inexplicable swings in blood glucose concentration, often resulting in ketoacidosis or hypoglycemic coma. These swings occur despite constancy in insulin injections, exercise, and diet [9]. These patients may require multiple or prolonged hospitalizations which disrupt daily life and cause mental and financial burden on the family and the healthcare system [7]. The diabetic state induced by total pancreatectomy is characterized by complete insulin deficiency (as confirmed by the absence of C-peptide in the serum), pancreatic polypeptide deficiency, and an absence of functional glucagon. Because the apancreatic state also results in a defect in gluconeogenesis secondary to hypoglucagonemia, daily insulin requirements in these patients are typically lower than in type 1 or type 2 diabetics [10, 11]. These patients also demonstrate increased insulin sensitivity secondary to increased expression of peripheral insulin receptors and enhanced plasma clearance of insulin. Hence, the therapeutic window to maintain euglycemia is narrowed, resulting in frequent episodes of mild to severe postprandial hypoglycemia following insulin administration [12].

Whereas patients with diabetes mellitus will often be chronically hyperglycemic, patients with brittle diabetes on insulin who are chronically hypoglycemic have been shown to initiate upregulation of cerebral endothelial glucose transporters [13]. Due to enhanced brain glucose uptake, counter-regulatory hormones are not secreted leading to systemic episodes of diabetic hypoglycemic unawareness in pancreatectomized individuals [14, 15].

Pertinent anatomy of pancreas

The mature pancreas is composed of morphologically and functionally distinct endocrine and exocrine components. The endocrine pancreas functions in a "checks and balances" system, the details of which are pertinent to the surgeon planning a TP and briefly reviewed.

Endocrine pancreas

The endocrine cells form aggregates scattered throughout the exocrine pancreas in the form of islets of Langerhans. The normal human adult pancreas contains about one million islets of Langerhans, constituting 2–3% of the gland's volume. A typical islet is composed of ~5000 endocrine cells. The islets contain five endocrine cell types—beta cells (β), glucagon-producing alpha cells (α), somatostatin-producing delta cells

(δ), ghrelin-producing gamma cells (γ), and pancreatic polypeptide-producing PP cells [16].

Insulin Insulin is a 51-amino acid peptide synthesized and secreted by the pancreatic beta cells throughout the pancreas. Insulin has a number of effects on glucose metabolism including inhibition of glucagon, glycogenolysis, and gluconeogenesis; increased glucose transport into fat and muscle via GLUT4; increased glycolysis in fat and muscle; and stimulation of glycogen synthesis [17–19]. Even partial pancreatectomy can decrease insulin secretion, leading to post-operative diabetes; however, in the setting of a total pancreatectomy, exogenous insulin treatment is necessary to control inevitable hyperglycemia.

Glucagon Glucagon is a 29-amino acid peptide synthesized from proglucagon in alpha cells located predominantly in the body and tail of the pancreas [20]. The function of glucagon is to increase blood glucose concentration via stimulation of hepatic gluconeogenesis and glycogenolysis, in addition to stimulation of insulin and somatostatin secretion [17, 21]. Glucagon decreases pancreatic juice volume, protein, amylase, and bicarbonate content. It has a complex role in positive and negative feedback loops to regulate glucose homeostasis, which is primarily why pancreatogenic diabetes is so labile/brittle after TP.

Somatostatin Somatostatin is present in δ cells of the islets, the small intestine, and in nerve terminals [22]. It is a potent inhibitor of insulin, glucagon, and PP secretion. Secretion of somatostatin is inhibited by insulin [23, 24]. Therefore, in the apancreatic state, this endocrine regulatory hormone is also unable to control glucose homeostasis.

Indications for TP

Due to long-term metabolic complications, difficulty in managing brittle diabetes, and the ensuing reduced quality of life, enthusiasm for TP has significantly waned over the last few decades [25]. However, advances in insulin formulations and modern pancreatic enzyme preparations have allowed sufficient control of endocrine and exocrine pancreatic insufficiency enabling a reasonable quality of life and decreased long-term morbidity. This, combined with improvement in the safety of pancreatic surgery, has decreased the morbidity and mortality of the procedure and reintroduced interest in TP in the treatment of pancreatic diseases [1, 26].

Premalignant lesions

Distinct non-invasive precursor lesions which can give rise to invasive carcinoma of the pancreas include pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasms (IPMNs) [27]. Patients with widespread and multifocal advanced pancreatic intraepithelial neoplasia may have a field defect in the gland that carry increased risk of progression to pancreatic adenocarcinoma. In highly selected patients, especially with a significant family history, prophylactic TP may be considered to avert the development of pancreatic carcinoma [28].

In addition, early studies of mucinous cystic lesions of the pancreas identified that approximately 30 to 40% of patients harbored an invasive malignancy at diagnosis. The remainder of patients in that report had intraductal micropapillary changes with atypia, dysplasia, or carcinoma in situ. The changes were multifocal and occurred throughout the gland; thus, it was defined that intraductal papillary mucinous neoplasms (IPMNs) were felt to represent a global disorder of the ductal epithelium and not just a localized defect [29]. In more modern series including updates to the original Sendai criteria, main duct IPMN, in particular, has been found to have significant risk of occult malignancy and malignant transformation. For patients with diffuse main duct IPMN along the length of the gland, current consensus from the International Association of Pancreatology IPMN working group and the European Study Group on Cystic Tumours of the Pancreas stipulate that TP may be selectively employed, particularly in high-risk IPMN with severe dysplasia at the surgical margin [30, 31]. For these high-risk lesions in few and limited highly selected individuals, TP is recommended until additional biomarkers reflective of the biology of disease can be identified [26, 31]. Similarly, for diffuse branch-duct IPMN with high-risk features or malignancy in multiple lesions spread throughout the gland, TP may be considered, though usually, each cyst may be individually considered for resection as an independent neoplasm [26, 31].

Familial pancreatic cancer

Familial pancreatic cancer implies that two or more first degree relatives experienced pancreatic cancer [32] and accounts for 3–10% of all cases of pancreatic cancer [33]. In familial disease, the risk of pancreatic cancer increases with the number of relatives affected. With one, two, and three affected family members, the risk of invasive disease is 4.6, 6.4, and 32 times for at-risk individuals [34]. Several pancreatic cancer hotspots have been identified, including both in high-penetrance genes such as *BRCA2*, *STK11*, *p16/CDKN2*, and *PALB2* and in low-penetrance genes such as the *ABO* blood group locus [35]. Though a very rare indication, and only in highly selected individuals from these hereditary pancreatic cancer families, total pancreatectomy may be considered to eliminate or decrease the risk of life threatening malignancy where there is widespread and multifocal neoplasia throughout the gland [36, 37].

R0 resection

For patients with localized pancreatic adenocarcinoma, positive resection margins are a negative prognostic feature [38–41]. Completion pancreatectomy has been shown to improve survival in isolated pancreatic neck margin positive patients and has been recommended if necessary to achieve R0 resection after pancreaticoduodenecomy [42]. Similarly, for main duct IPMN with high-grade dysplasia at the margin, completion pancreatectomy or further resection to a negative margin may be considered. In many cases, simply extending the resection may avoid the need for total pancreatectomy and achieve negative margins, though in cases where arterial resection is necessary, total pancreatectomy may be performed to reduce the risk of pancreatic fistula induced pseudoaneurysm of a fresh vascular anastomosis in high-risk patients [37]. Furthermore, in highly selected patients with pancreas only metastases, most often from renal cell carcinoma, total pancreatectomy may be indicated after multidisciplinary discussion [43, 44].

Pancreatic fistula

Pancreatic fistula is a known complication after partial pancreatectomy [45–48]. Techniques of pancreatico-enteric reconstruction have been extensively studied and have reduced but not eliminated the risk of pancreatic leak. Prognostic factors for pancreatic anastomosis failure are well known including small pancreatic duct, soft gland texture, surgical technique, and extent of resection [49–53]. Though the majority of pancreatic fistulae will heal with appropriate drainage and clinical management, surgical intervention is occasionally necessary i.e., in type C fistulas. In instances when the patient condition or tissues are not amenable to creating a new anastomosis, or in the situation of peritonitis or bleeding, the safest procedure to eliminate pancreatic fistula may be completion pancreatectomy.

Chronic pancreatitis

Pain is the most common indication for surgery in patients with chronic pancreatitis, usually when it is recalcitrant to management with analgesics and pancreatic enzymes [54]. Although not very well understood [55], compartment syndrome, which is probably caused by elevated pressure in the main pancreatic duct, might be the origin of the pain [56–58]. Total pancreatectomy remains controversial as treatment for chronic pancreatitis but has a role in patients with severe pain resistant to other medical and surgical procedures and for significant intraductal obstruction not amenable to pancreatic surgical drainage procedures [56–59].

Neuroendocrine tumors

Pancreatic neuroendocrine tumors are rare neoplasms, and represent around 1–2% of all pancreatic tumors with an incidence of approximately 1/100,000 population. Surgical treatment for pancreatic neuroendocrine tumors varies according to site and size of tumor, if it is single or multiple, if it is benign or malignant, and if it is associated with multiple endocrine neoplasia (MEN) type 1 [60–63]. TP has a role in surgical management of recurrent, multicentric, and locally advanced neuroendocrine tumors [64, 65].

Nesidioblastosis

Nesidioblastosis is a condition that is characterized by hypertrophy and hyperplasia of the islets of Langerhans. It can result in persistent hyperinsulinemia with hypoglycemia and is the leading cause of hyperinsulinemic hypoglycemia in childhood, whereas in adults, it represents 0.5–5% of cases [66, 67]. Early diagnosis of this condition in infants is essential because it may lead to cerebral palsy, impaired mental development, epilepsy, or other forms of irreversible brain damage [68, 69]. Recent associations with bariatric surgery have also been identified. Near total pancreatectomy (95% resection) should be considered early when this condition is resistant to standard medical management and often results in difficult to control diabetes [70, 71].

Morbidity and mortality of post-pancreatectomy diabetes

Currently, elective TP leads to perioperative morbidity and mortality comparable to that of the other pancreatic resection procedures and without the major morbidity of a pancreatoenteric anastomosis. Despite limitations caused by the ensuing insulin-dependent diabetes, the overall quality of life is acceptable, and the limitations do not justify avoiding TP in patients in whom the complete removal of the pancreas would be beneficial [25, 26, 72].

The diabetes post-TP is characterized by frequent hypoglycemic episodes and severe malabsorption owing to exocrine insufficiency [25, 73–77]. Other metabolic consequences include osteoporosis, osteopathy, and hepatic dysfunction [25, 74].

Mortality rates vary from 0 to 8% and morbidity rates vary from 25 to 45% [25, 42, 73, 78–80].(Table 1). Pancreatogenic diabetes remains a major source of morbidity. It leads to frequent episodes of hypoglycemia and or ketoacidosis that can be difficult to control [74]. In a study from the Mayo Clinic, 79% of TP patients reported hypoglycemic episodes, 41% experienced severe hypoglycemia, and 4% developed DKA [82]. Barbier and colleagues reported that 40% of TP patients experienced loss of consciousness owing to hypoglycemia, and had a median of 10 episodes per month [79]. Overall mortality and morbidity of TP, as well as brittle diabetes-specific mortality and morbidity rates,

Table 1 Diabetes-related mortality after total pancreatectomy

Author	Number	Mortality (%)	Morbidity (%)	Diabetes
Crippa et al. [78]	65	0	39	No deaths due to hypoglycemia
Billings et al. [73]	99	5	32	3 deaths due to hypoglycemia
Schmidt et al. [42]	33	6	36	–
Casadei et al. [80]	20	5	25	No deaths due to hypoglycemia, 23% readmission for blood glucose issues
Muller et al. [25]	147	5	40	No deaths, 8.3% readmission for blood glucose control
Barbier et al. [79]	56	3.6	45	2 deaths due to blood glucose issues
Watanabe et al. [81]	44	5	32	1 death due to diabetic ketoacidosis

are summarized in Table 1. Hospital readmission rates up to 16% due to of complications of pancreatogenic diabetes can be expected after TP [25].

HbA1c levels can be used as an indication of glycemic control over the previous 60 days for patients after TP [83]. Elevated levels of 6.7–11% have been reported [25, 74, 77, 78, 84, 85] though recent studies reflect lower HbA1c levels believed to be due to advances in diabetes management [82]. This is reflected in a recent study by Roberts and colleagues who reported almost no difference in diabetes-specific outcomes or control as assessed by a diabetes-specific questionnaire [86].

Weight loss is common after TP in 40 to 85% patients. With an average weight loss of 7.5 kg [25, 73, 74, 78–80, 82]. Quality of life (QoL) does remain an issue after TP. Though Muller et al. reported comparable global health status of patients after TP compared to a control group undergoing pancreaticoduodenectomy using a robust QoL questionnaire [25], Barbier et al. reported a global health quality of life score of 64 (0–100) after TP [79]. In general, with appropriate glucose management strategies, QoL after TP may be comparable to QoL after partial pancreatectomy [87].

Management

Management is based on patient education, glycemic control, and close collaboration between the surgeon, endocrinologist, and other key healthcare providers including outpatient clinic nurses and dieticians.

Education

The first priority in regard to treatment is to ensure that the patients have sufficient education in the management of their diabetes [88]. A thorough practitioner explanation and demonstrated patient comprehension of the physiology of pancreatogenic diabetes is critical. Preoperatively, patients should be evaluated by an endocrinologist and taught how to self-administer insulin and to perform blood glucose monitoring. We feel that inabilities to perform these tasks, or a lack of understanding on the part of the patient and/or the family, are contraindications for recommending or performing TP. It is critical to identify patients preoperatively who are incapable or non-compliant, for any reason, of having an ability to monitor and maintain glycemic control. Patients are educated regarding hypoglycemia and the use of glucose tablets. Data supports improved outcomes with follow-up for outpatient diabetes education with their dietician and endocrinologist [89]. An important consideration in some difficult to control cases, however, is that long-term avoidance of hypoglycemic episodes is a primary concern, and both patient and endocrinologist expectations of glucose set-points may need to be liberalized on an individual basis for patient safety and quality of life, though at the possible risk of added secondary long-term hyperglycemic complications. Furthermore, in addition to education on glycemic control, the importance of appropriate caloric intake is important to review with the patient, including recommendations for a mixture of short- and long-acting carbohydrates, adequate protein intake based on their weight, and small, but frequent meals.

Insulin therapy

Insulin can be delivered in secondary diabetes by means of insulin pumps/continuous subcutaneous insulin infusion (CSII) or multiple daily insulin injections (MDII) [90]. Unfortunately, all large diabetes clinical trials studying glycemic control have excluded patients with pancreatogenic/type 3c diabetes. In the absence of generally accepted guidelines for the management of these patients, it is has been consistently recommended, including by the PancreasFest Recommendation Conference, that insulin dosing guidelines for type 1 diabetes mellitus be followed [91, 92]. After pancreatectomy, continuous insulin infusion at 0.1 U/kg/h should begin along with dextrose fluids (D5NS to provide 150 g/24 h), requirements thereafter calculated, and then 60–80% replaced in the subsequent days by one half basal (most commonly glargine insulin) and one half immediate release insulin formulations (most commonly aspart or lispro insulin). It is imperative to administer the basal insulin dose 1–2 h before discontinuation of insulin

infusion. Basal doses are then increased by 2 U q3d until fasting levels are appropriate. If fasting glucose is <70 mg/dl, then the basal dose is decreased by 4 U. If glucose is 70–130, then the same dose is continued. Blood sugars are checked a minimum of four times a day before each meal and at bedtime. The glycemic goals for hospitalized patients are 140–180 mg/dl, preprandial <140 mg/dl and maximum blood sugar <180 mg/dl [93, 94]. Insulin treatment with a basal formulation of glargine has markedly improved glycemic control in these patients. This recombinant, long-acting formulation has become increasingly available and allows a slow and steady absorption profile that limits peaks and troughs in insulin levels, thereby enabling most patients to achieve acceptable glycemic control [26]. When discontinuing intravenous insulin, this type of transition protocol is associated with less surgical morbidity/mortality and lower costs of care [95]. In our experience and based on a combination of the 2009 and 2017 American Diabetes Association guidelines, this simple and effective post-operative treatment algorithm for patients after TP is efficient and effective [93, 94]. It should be mentioned that these protocols are based on data from type 1 diabetes patients, and not only will less insulin likely be necessary to achieve the same glycemic set-points in apancreatic patients, but extra care and consideration for acceptance of permissive hyperglycemia may be acceptable to repeated episodes of hypoglycemia in this patient population on a per-patient basis.

Jethwa et al. reported that TP patients required a median starting insulin dose of 34 U (range 8–88 U) daily and median dose of 46 U (range, 8–88 U) after optimization [77]. In the Mayo clinic series, daily mean insulin requirement of 32 U daily was reported (range, 2–66 U) [73]. Data regarding the number of hypoglycemic episodes and predicted daily insulin requirements after total pancreatectomy are summarized in Table 2.

Patients may be transitioned to insulin pumps/CSII for optimization of glucose control and improvement in life style. CSII is the "gold standard" of basal insulin replacement and has the unique ability to deliver insulin in a continuous mode mimicking the endogenous insulin production of the pancreas. The rate of basal insulin by CSII can be delivered according to the patient's needs. This approach is successful because CSII infuses reliably even at low rates of 0.05–0.1 U/h. An insulin to carbohydrate ratio and a correction factor (sensitivity factor) is used to individualize a patient's insulin requirements based on the number of carbohydrates one consumes per meal while on the pump [96]. This outpatient strategy is a logical extension of the perioperative continuous post-operative blood glucose monitoring randomized controlled trial performed using an "artificial pancreas" that showed excellent glycemic control after pancreatic resection [97].

In most patients on CSII, mean blood glucose concentrations and glycated hemoglobin percentages are either slightly lower or similar to multiple insulin injections. However, hypoglycemia is markedly less frequent than during intensive injection therapy. Ketoacidosis occurs at the same rate. Nocturnal glycemic control is improved with insulin pumps, and automatic basal rate changes help to minimize the pre-breakfast blood glucose increase (the "dawn phenomenon") often seen with injection therapy [98].

Papygyri et al. reported the experience with use of continuous subcutaneous insulin infusion in 112 type 1 diabetic patients followed for 7 years and previously treated with multiple daily insulin injections (MDII). HbA1c decreased by 0.6–0.9% [99]. Several other studies have shown that CSII results in better glycemic control than multiple injections, with an improvement of HBA1c of 0.2–0.4%, with a decrease in hypoglycemic events [98, 100–105]. Hirsch et al. evaluated CSII of insulin aspartame versus MDII of insulin aspartame/insulin glargine in type 1 diabetic patients previously treated with CSII [106]. They found that CSII therapy resulted in lower glycemic exposure without increased risk of hypoglycemia, as compared with MDI. The main complication reported with CSII, mainly at the start of the treatment, is hypoglycemic episodes. Specific patient training and fine adjustment of insulin infusion doses are often sufficient to minimize this complication [99].

Real-time continuous glucose monitors are also being used for better glucose control. They check interstitial glucose levels every 5 min and provide 288 blood glucose readings daily along with graphs to give patients a better sense of their

Table 2 Number of hypoglycemic episodes and predicted daily insulin requirements after total pancreatectomy

Author	Number	Episodes of hypoglycemia	HbA1c levels (%)	Median insulin requirement, U/day (range)
Crippa et al. [78]	65	0–5/week	56% between 7 and 9% 11% > 9%	32 (18–52)
Billings et al. [73]	99		5.0–11.3%	32 (2–66)
Casadei et al. [80]	20	1–10/week	5.2–10.3%	25 (20–52)
Muller et al. [25]	147	–	6.7–7.5%	–
Barbier et al. [79]	56	1–36/month	6.3–10.3%	16 (7–48) long acting and 21 (7–70) rapid acting
Watanabe et al. [81]	44	12/week	6.2–11.2%	6 (0–16) long acting and 17 (10–28) rapid acting

sugars. This may enable them to adjust their insulin requirements and also prevent the frequency and the severity of hypoglycemia. In a randomized trial of 322 adults and children with type 1 diabetes and baseline A1C level ≥ 7.0%, the Juvenile Diabetes Research Foundation (JDRF) Continuous Glucose Monitoring Study Group reported that real-time continuous monitors substantially improved A1C levels without increasing the frequency of hypoglycemia in adult's ≥25 years of age [107].

It should be considered, however, that the role of CSII and insulin pumps specifically after TP is not well studied, and much of the data is from the type 1 diabetes literature. These patients clearly have less of a risk of hypoglycemia compared to TP patients, and thus, the data available to the surgeon and endocrinologist in using this strategy after TP is useful to extrapolate from, but remains limited.

Hypoglycemia

As mentioned, there remains the risk of hypoglycemia in these patients. Asymptomatic hypoglycemia (<70 mg/dl) should be treated with carbohydrate ingestion and adjustment of the insulin regimen [108]. Symptomatic patients should treat themselves with 15–20 g of a fast acting carbohydrate (fruit juice, glucose tablet, or hard candy), and severe hypoglycemia may require administration of glucagon (0.5–1 mg). If needed, it is typically administered intramuscularly, though a recent trial demonstrated similar efficacy in rescue with both intranasal and intramuscular glucagon [109]. That glucagon treatment is sometimes required and may need to be administered by someone other than the patient underscores the importance of education and assessment of both comprehension and home support in evaluating the patient for suitability for TP. Though glucagon replacement therapy has been attempted in small numbers of apancreatic patients [110, 111], with adequate education, insulin adjustment based on carbohydrate/total caloric ratios, and the more recent formulations and use of long-acting basal insulin, in our experience, it is rarely needed and certainly not routinely.

Islet cell transplantation

Islet cell transplantation (ICT) is a promising procedure for treatment of diabetic patients with brittle diabetes. The indications include hypoglycemic unawareness (i.e., onset not felt with glucose level ≤54 mg/dl) and/or metabolic lability (i.e., two or more severe hypoglycemic or ketoacidosis episodes requiring third party assistance within 1 year) and progressive chronic complications despite intensive insulin treatment [112]. Since 1999, allogenic islet transplantation data from North America, Europe, and Australia were submitted to the Collaborative Islet Transplantation Registry (CITR). Twenty-five US/Canadian medical institutions, two European centers, and an Australian center participated. The study reported that 71% of these patients were insulin independent at 1 year and 52% remained insulin independent at 2 years. Islet transplantation markedly reduced the occurrence of severe hypoglycemic events from more than 60% before transplant to <10% after 5 years. Islet transplantation also substantially improved HbA1c levels [113, 114]. In addition, in the recently reported phase 3 trial of islet cell allotransplantation by the Clinical Islet Transplantation (CIT) Consortium for patients with type 1 diabetes, the primary endpoint of achieving HgA1c levels of ≤7% was achieved in ~88% of patients, as was the goal of decreasing severe hypoglycemic events [115]. Insulin independence at 1 year was 52 and 42% at 2 years in this study, further supporting both previous trials and continued research of this intervention for this indication.

However, in addition to limited resources and availability, there are several limitations to ICT including the need for several donors for sufficient islet yield, the risks of lifelong immune suppression, and the progressive loss of islet function over time [116]. β cell regeneration from naïve pancreas and β cell generation from embryonic stem cells or induced pluripotent stem cells are potential approaches to manage diabetes after TP on the horizon. [117].

It is critical to note, however, that islet cell transplantation after surgery is primarily intended after TP only for highly selected patients with chronic pancreatitis, which is even more selective for allotransplantation in this disease, which in some institutions is only 1% of all considered cases [118, 119]. The issue with autotransplantation after resection of malignant or diffuse mucinous tumors is the potential seeding of malignant or premalignant cells. Thus, most centers consider this an absolute contraindication to autotransplantation [120], though a recent series of 31 patients with malignant pancreatic/ampullary disease have undergone the procedure [121]. In regard to islet allotransplantation, one of the main concerns is the obligatory immunosuppression and the risk of inducing malignancy [122], which is only further compounded in the setting of pancreatic neoplasia, and thus almost universally avoided therein. This limitation of immunosuppression is shared whether the allotransplant is of islets or the gland. An advantage of whole gland allotransplant theoretically is concomitant correction of exocrine insufficiency; however, data is limited comparing islet to gland transplantation after TP in terms of glycemic control, though graft survival rates of >75% can be achieved in this setting [123].

Conclusions

Oncologic indications for total pancreatectomy have increased. We found that there was a paucity of information on endocrine management of TP in this setting, particularly in the surgical literature, and that there was a need for a

straightforward and easy to follow algorithm for surgeons to manage patients post-operatively after TP. This study is limited by a lack of randomized controlled trials, systematic reviews, or large cohort studies to address the endocrine needs of patients after TP in the literature. As a result, the review is limited to case series, observational studies, and extrapolation of data from type 1 and 2 diabetes; thus, the level of evidence of the available data is low, limiting the strength of our recommendations. This limitation spotlights the critical need for a systematic review of this nature; therefore, the available data was comprehensively summarized for the practicing pancreatic surgeon. The causes of brittle diabetes after TP were reviewed as they pertain to the pertinent anatomy and physiology of the endocrine pancreas, and the significance of the ensuing morbidity and mortality was highlighted. Strategies to reduce hyper- and hypoglycemic episodes depend greatly on patient education, and patients unable to comprehend treatment algorithms or to be compliant with outpatient visits and blood glucose management strategies are not recommended for TP. Close outpatient follow-up with endocrine nurses and dieticians have improved outcomes, as have personalized insulin therapies, especially with continuous subcutaneous insulin injections and real-time continuous glucose monitoring. A practical post-operative treatment algorithm based on the limited available data has been devised and is currently employed at our center. Future strategies may include more widespread use of islet transplantation (in non-neoplastic settings) or beta cell generation from stem cells.

Acknowledgements The authors would like to acknowledge Daphne O'Reilly MD and Maria Ferrera MD for their contributions to this project. Dr. Maker is supported by the NIH/NCI K08CA190855.

Authors' contributions Study conception and design—AVM; acquisition of data—RS, AVM, and VB; analysis and interpretation of data—RS, AVM, and VB; drafting of manuscript—RS and AVM; critical revision of manuscript—RS, AVM, and VB.

Compliance with ethical standards

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

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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