Curr Diab Rep (2015) 15: 16
DOI 10.1007/s11892-015-0589-2

OTHER FORMS OF DIABETES (R BONADONNA, SECTION EDITOR)

Diabetes After Pancreatic Surgery: Novel Issues

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Published online: 22 February 2015

Abstract In the developed world, pancreatic surgery is becoming more common, with an increasing number of patients developing diabetes because of either partial or total pancreatectomy, with a significant impact on quality of life and survival. Although these patients are expected to consume increasing health care resources in the near future, many aspects of diabetes after pancreatectomy are still not well defined. The treatment of diabetes in these patients takes advantage of the therapies used in type 1 and 2 diabetes; however, no specific guidelines for its management, both immediately after pancreatic surgery or in the long term, have been developed. In this article, on the basis of both the literature and our clinical experience, we address the open issues and discuss the most appropriate therapeutic options for patients with diabetes after pancreatectomy.

Keywords Pancreatectomy · Pancreatogenic diabetes · Pancreatic cancer · Islet autotransplantation

This article is part of the Topical Collection on *Other Forms of Diabetes*

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Introduction

Pancreatic surgery has been described as a formidable feat, and for this reason, its history is relatively brief, with the first attempts to pancreatic surgery being reported in the late 1800s.

Although the pancreas was first described by Herophilus in the 4th century B.C., the very nature of this organ, its histology, and functions have been for centuries essentially unknown. One of medical history's most prominent figures may have contributed to this oblivion: Galen, the most renowned physician of ancient Rome, is said to have described the pancreas as merely a fatty pad placed in front of the major blood vessels of the abdomen for their protection. At that time, long before Galileo's introduction of the experimental method as the basis of scientific knowledge, Galen's word was law. Therefore, for many centuries, no further attempts were made at investigating the pancreas, its physiology, or pathology until the Renaissance [1]. In 1642 in Padua, a center of excellence for medical studies, Johann Georg Wirsung, while dissecting the cadaver of a criminal executed by hanging the day before, first described the main pancreatic duct, which since then has been named after him. Perhaps anticipating the significance of his discovery, he engraved a drawing of pancreas anatomy in copperplate and sent it to several influential anatomists of the time, thus ensuring himself credit as the first to describe the main pancreatic duct. Although Wirsung's discovery ensured that his name is still remembered today, it had more immediate, negative repercussions on his life, if we believe the rumors of those times. Wirsung was in fact assassinated in 1643, possibly during a heated discussion over his discovery, perhaps by a colleague or a student who assisted him during that specific dissection and later claimed the discovery as his own [2]. The study of the pancreas proceeded slowly until the second half of the 19th century when Paul Langerhans Jr., then a student at Virchow's Institute in Berlin, discovered islets of endocrine tissue producing insulin embedded in the

exocrine pancreatic tissue [3]. If the understanding of pancreatic physiology advanced slowly, attempts to conduct pancreatic surgery lagged even further behind. The pancreas anatomical position deep within the abdomen in the retroperitoneal space, behind the stomach and intestinal loops, in close proximity to the aorta, vena cava, and the emergence of their principal branches to the abdominal organs, the spleen and kidneys made it virtually unreachable at times when even the simplest surgical procedure was burdened by many severe risks. Thus, pancreatic surgery perhaps more than other type of surgery is indebted to the significant advances in the fields of anesthesiology and antisepsis. The first distal pancreatectomy was attempted in 1882 by Friedrich Trendelenburg, with only 21 surgeons following his steps with 24 pancreatic resections over the next 20 years. All the reported resections were limited to the body or tail of the pancreas or consisted in the enucleation of a mass. The first pancreaticoduodenectomy was attempted in 1898 by Alessandro Codivilla in Bologna in a patient with pancreatic carcinoma, with various attempts made in the following years to develop surgical techniques to resect portions of the pancreas and duodenum, although at that time it was believed that the complete resection of the duodenum was incompatible with patient survival [4]. Allen O. Whipple was the first surgeon to attempt a pancreaticoduodenectomy with the complete excision of the duodenum, publishing in 1935 the results of his first three pancreaticoduodenectomies [5] and becoming the undisputed father of modern pancreatic surgery. All these interventions preserved at least a small portion of the pancreas, or they would have been otherwise fatal, since insulin was yet to be discovered.

Diabetes mellitus has been known for thousands of years, but the involvement of the pancreas is relatively recent. In 1889, von Mering and Minkowski demonstrated that the excision of the whole pancreatic gland from dogs made them diabetic. In this way, they demonstrated the central role of the pancreas in regulating glucose levels and described a new type of diabetes, the "pancreatogenic diabetes" [6]. All this occurred well before the discovery of insulin in 1921 by Banting and Best (for which Banting was awarded a Nobel prize in Medicine and Physiology) [7]. Since then, insulin has been saving the life of thousands of patients and opening the doors to breakthrough scientific discoveries, including the determination of insulin molecular structure by Frederick Sanger (Nobel prize in Chemistry in 1958), the insulin crystal structure by Dorothy Crowfoot Hodgkin (Nobel prize in Chemistry in 1964), and the first radioimmunoassay by Rosalyn Yalow (Nobel prize in Medicine and Physiology in 1977), use of recombinant DNA technology for mass production of a drug in the 1980s [8]. In humans, the first case of a pancreatic diabetes mellitus was described at the Saint Mary's Hospital in Rochester, Minnesota, on July 14 1942 [9], where the first total pancreatectomy was performed.

Today, the number of patients undergoing pancreatic surgery is increasing, owing to early diagnosis of premalignant lesions [10] and referral of patients with surgically treatable pancreatic diseases to high-volume institutions [11, 12]. Pancreas surgery is still considered as major abdominal surgery and, thus, burdened by a significant rate of complications [13, 14, 15•], including death [16]. Fortunately, the development of surgical expertise and centralization of pancreatic surgeries in high-volume centers has resulted in a steep decline of mortality rates, from the 25 % reported in the initial series of the 1960s to the current rate of less than 3 % [16, 17], although with still a consistent gap between high-volume and low-volume centers [12, 16, 18–20]. As the survival of these patients has increased because of new chemotherapy strategies for cancer patients [21•, 22], attention has shifted to quality of life [23–27]. Among the possible complications of pancreatic surgery, diabetes mellitus certainly ranks high because of high prevalence [28•, 29•], likelihood of acute events (i.e., hypoglycemic episodes) [30], and long-term complications (i.e., nephropathy, neuropathy and retinopathy) [31–40], which today, patients are more likely to experience because of increased life expectancy after pancreatic surgery.

Diabetes After Pancreatic Surgery: a Specific Entity

Diabetes following pancreatic surgery is currently classified as a subtype of secondary or type 3 diabetes mellitus (T3cDM) [41]. Total pancreatectomy always results in postsurgical diabetes, unless the patient receives a concomitant islet transplant. Diabetes after total pancreatectomy has quite distinct features from both T1D and T2D [29•, 42, 43, 44•, 45•, 46–53] (see Table 1). In contrast to T1D, patients with pancreatogenic diabetes rarely develop ketoacidosis, and hyperglycemia is usually mild in most cases [54]. Unlike patients with T2D, patients undergoing major pancreatic resection are quite sensitive to exogenous insulin [55], and episodes of iatrogenic severe hypoglycemia are common [30, 56]. Numerous studies have been carried out to elucidate the metabolic changes induced by total pancreatectomy, changes which extend well beyond insulin and glucagon deficiency. Nosadini et al. studied insulin action after pancreatectomy prompted by the increased sensitivity to insulin observed in these patients [55]: enhanced extrahepatic tissue sensitivity to physiologic hyperinsulinemia and higher insulin binding to red blood cell receptors were observed [57]. The increase in insulin binding was due to an increase in peripheral insulin-binding sites, rather than increase in receptor affinity. Moreover, the plasma clearance rate of insulin was significantly higher in patients with total pancreatectomy than in patients with T1D. Thus, the upregulation of peripheral insulin receptors in response to

Table 1 Laboratory, metabolic, and clinical features of the different types of diabetes mellitus

	T1D	T2D	Diabetes after pancreatic surgery
Hormone levels			
Insulin	Low	High	Low/absent
Glucagon	Normal/high	Normal/high	Low/absent
Pancreatic polypeptide	Normal/low (late)	High	Low
Glucose-dependent insulinotropic polypeptide	Normal/low	Normal/low	Low (duodenectomy)
Glucagon-like peptide 1	Normal	Normal/low	Normal/high
Insulin sensitivity			
Peripheral	Normal/high	Normal/low	Normal/high
Hepatic	Normal	Normal/low	Low
Clinical features			
Hyperglycemia	Severe	Usually mild	Mild
Hypoglycemic episodes	Common	Rare	Common
Ketoacidosis episodes	Common	Rare	Rare

insulin deficiency makes patients uniquely sensitive to hormone replacement [55]. Despite an increase in peripheral insulin receptor availability, pancreatogenic diabetes is characterized by a decrease in hepatic insulin receptor availability [58]. This paradox is due to the concurrent deficiency of pancreatic polypeptide [59–61] causing the liver to be resistant to the insulin suppression of hepatic glucose production [62, 63].

Hepatic glucagon responsiveness is also enhanced in pancreatogenic diabetes [64, 65]. Bajorunas et al. showed that the metabolic response to glucagon was considerably more pronounced in patients with diabetes after total pancreatectomy than in patients with T1D [64]. Therefore, chronic glucagon deficiency may modify the liver sensitivity to glucagon, presumably through the upregulation of glucagon receptors, which, in turn, enhances the response to hyperglycemia. Obviously, the absence of glucagon secretion after total pancreatectomy exposes patients to an increased risk of severe hypoglycemia because of the loss of this important counterregulatory mechanism [66]. Hypoglycemic episodes and exogenous insulin requirement in pancreatogenic diabetes are also the consequence of the exocrine insufficiency [67]. In fact, rapid intestinal transit because of pancreatic exocrine insufficiency makes glucose absorption unpredictable, increasing the risk of insulin-induced hypoglycemia [68]. Furthermore, the secretion of the enteric glucoregulatory hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) is also impaired in pancreatogenic diabetes [69]. A marked decrease in GIP secretion was indeed reported in these patients, presumably because of duodenectomy with shunting of chime to a more distal part of the jejunum where the GIP-producing K cells are fewer than in the proximal part of the small intestine. A remarkable increase in GLP-1 was also described after total pancreatectomy, with levels comparable with those observed after gastric bypass surgery [70]. Similarly to the GIP decrease, also the GLP-1 increase is likely a direct consequence of duodenectomy, with the delivery of nutrients to portions of the gut where the density of the GLP-1–producing L cells is higher than in the proximal small intestine [71]. Finally, the secretion of GIP and GLP-1 has been shown to be dependent also on the absorption of nutrients, with a documented increase in GIP and GLP-1 responses to oral nutrients during pancreatic enzyme replacement [72].

Diabetes After Pancreatic Surgery: Prevalence and Incidence

While data on prevalence and incidence of T1D and T2D are available for different geographical areas worldwide, specific data on the incidence and prevalence of T3cDM are rare [73–75], and those for diabetes after pancreatic surgery hardly exist. Old studies estimated that 0.5–20 % of the patients with a diagnosis of diabetes has T3cDM, with significant regional differences: about 0.5–1.15 % of all cases of diabetes in North America and 15–20 % in Southeast Asia, where tropical or fibrocalcific pancreatitis is endemic [73]. In 2005, an epidemiological study of pancreatic diabetes in Japan estimated a prevalence of T3cDM of 15.2 per 100,000 individuals and an incidence of 1.1 new cases per 100,000 individuals per year [75]. More recently, T3cDM was reported to account for 5–10 % of the patients with diabetes in western countries [44•, 74, 76]. As for the causes of T3cDM, pancreatic surgery is responsible for 2–10 % of the cases of T3cDM [74, 75].

The incidence of diabetes after pancreatic resection may be greater than estimated. After total pancreatectomy, the incidence of postsurgical diabetes is 100 % [36]. According to the Nationwide Inpatient Sample from 1998 to 2006, an

estimated 4013 weighted patient-discharges for total pancreatectomy occurred in the USA [77], and the number of total pancreatic resections performed each year is growing. Over the decade 2003–2012 in Italy, 2018 patient-discharges for total pancreatectomy were recorded, with almost doubling of the cases between 2003 and 2012. The risk of developing glucose intolerance or overt diabetes has also been estimated for patients after partial pancreatic resections, and specific risk factors for diabetes have been identified in these patients [78••]. The incidence of diabetes after partial pancreatectomy varies greatly depending on the underlying disease and the portion of the pancreas being removed, both associated with the endocrine function of the residual pancreatic parenchyma. For example, shortly after distal pancreatectomy, 14 % of the patients who had a pancreatic tumor removed developed diabetes compared to 39 % of those with chronic pancreatitis [79]. Similarly, for proximal pancreatectomy, 15–40 % of the patients with chronic pancreatitis develop diabetes shortly after surgery (and the incidence might be further reduced using duodenum-preserving techniques), compared to 18–27 % of those with pancreatic head resection for benign tumors, although the estimates are less solid because data are limited [29•]. Central (middle) pancreatectomy is not associated to an increased risk of diabetes. However, pancreatic fistulae, a relatively common complication of central pancreatectomy, may have an increased risk of diabetes after surgery. Although no clinical study ever compared the risk of diabetes after central pancreatectomy in patients with or without pancreatic fistula, we may speculate that local inflammation damages the residual parenchyma thus impairing endocrine function. An additional important aspect to consider when assessing the burden of diabetes after partial pancreatectomy is the duration of postsurgical follow-up: while shortly after partial pancreatectomy, 8–23 % of the patients have pancreatogenic diabetes, this proportion increases to 30–50 % during follow-up [45•]. Recently, we reported that 21 % of the patients undergoing partial pancreatectomy experiences new onset diabetes and 30 % of those with diabetes prior to surgery had worsening of glucose control [29•]: because of a median follow-up of 2.2 years, we may have underestimated the true incidence of pancreatogenic diabetes.

Over the decade 2003–2012 in Italy, 27,879 patient-discharges for partial pancreatectomy (including duodenopancreasectomy) were recorded, with a 31 % increase of the cases between 2003 and 2012.

Based on what we reported in our cohort of patients undergoing pancreatic surgery [28•], we estimate that the proportion of new cases of diabetes after partial pancreatectomy is on average 13 %.

Brittle Diabetes After Total Pancreatectomy: Myth or Reality?

Patients with diabetes following total pancreatectomy are generally considered difficult to manage, with potential life-threatening acute complications [79–82]. Up to 25 % of the patients with pancreatogenic diabetes have "brittle diabetes" [83–88], with rapid swings of glucose levels from hyperglycemia because of unsuppressed hepatic glucose production to severe hypoglycemia after administration of exogenous insulin because of the lack of glucagon response. Repeated hypoglycemic events may result in hypoglycemia unawareness because of the progressive decrease of the glucose threshold triggering symptoms [89]. Moreover, total pancreatectomy is associated with the resection of the duodenum, gallbladder, distal common bile duct, and often distal stomach. The consequences of such extensive ablative surgery consist not only in pancreatic hormone deficiency but also in the derangement of gut hormones important for metabolism [90, 91]. However, several authors have recently reported that the glycemic control of patients with diabetes after total pancreatectomy has improved compared to what was reported in earlier studies [31, 36, 92–95]. Several factors may explain these changes overtime. In recent years, insulin-dependent diabetes and malabsorption can be controlled more effectively than in the past with new drugs, including insulin analogues [36, 96]. Moreover, the rate and the severity of hypoglycemia are affected by the underlying pancreatic disease. For example, in patients undergoing total pancreatectomy for alcoholic chronic pancreatitis, hypoglycemic events are more frequent and severe if alcohol abuse persists. Finally, improving patients' awareness and compliance irrespective of the social–economic class, increasing referrals to a diabetes center, and the widespread use of glucose meters for measuring capillary glucose may all have contributed to the improvement of glycemic control and stability overtime. However, although there are no large prospective controlled clinical trials estimating the true incidence of brittle diabetes after total pancreatectomy, we acknowledge that in clinical practice, the diabetes management of these patients is often still problematic, especially in relatively young individuals where the risk of developing chronic complications later in life has to be carefully balanced against the risks of repeated life-threatening severe hypoglycemia.

Diabetes After Pancreatic Surgery: Do Late Complications Exist?

There is still a debate about the burden of macrovascular and microvascular complications in patients who developed diabetes after pancreatic surgery [97–99]. The underlying pancreatic disease and the relatively short duration of follow-up make it difficult to estimate incidence and prevalence of

diabetes complications in these patients. The microvascular complications may be encountered in T3cDM as often as in T1D [97–100]. Therefore, we may assume similar rates in patients with diabetes after pancreatic surgery. In fact, the incidence of retinopathy is reported similar to that observed in T1D and its prevalence increases with diabetes duration [98, 99, 101••, 102]. Sporadic cases of diabetic glomerulosclerosis have been described in patients with total pancreatectomy, but there is no report of end-stage diabetic kidney disease. In diabetes secondary to pancreatic disease (i.e., not limited to pancreatic surgery), early signs of renal dysfunction such as microalbuminuria or glomerular hyperfiltration are observed similarly to what is reported in T1D [103], while macroalbuminuria and overt renal disease are unusual. Neuropathy is also described as a common complication of pancreatogenic diabetes. There is the general idea that pancreatogenic diabetes is not associated with macrovascular complications. This is because concomitant exocrine pancreatic insufficiency cholesterol levels and caloric intake are low, therefore reducing cardiovascular risk. However, with the increasing life expectancy, cases of diabetic macrovascular complications have been reported in patients after pancreatic surgery [104–107]. Taken together, these data support the need to treat patients with diabetes after pancreatic surgery with the goal of preventing long-term complications while minimizing the risk of life-threatening severe hypoglycemia [31–40].

Diabetes After Pancreatic Surgery: Clinical Management

In the absence of specific guidelines for patients who developed diabetes after pancreatic surgery, diabetes after pancreatectomy is treated similarly to T1D and T2D. In this section, we will discuss specific aspects of the treatment of diabetes after pancreatectomy that, in our opinion, deserve attention.

1. Treating hyperglycemia immediately following pancreatectomy

   There is a general agreement that following major surgery (including cardiac, general, vascular, and orthopedic surgery), postoperative hyperglycemia is an independent risk factor for increased morbidity and mortality [108]. Furthermore, a detrimental effect of high-glucose variability has been described in critically ill patients and patients in surgical intensive care unit [109–111, 112••, 113]. Concordantly, early postoperative hyperglycemia and high-glucose variability were recently associated with postoperative complications after pancreatoduodenectomy [114••]. Consequently, postoperative intensive insulin therapy should be the standard treatment for patients undergoing pancreatic surgery, with a target blood glucose level of less than 140 mg/dL [114••, 115]. This glucose goal appears more stringent than the one generally suggested. In fact, the general consensus is that intensive insulin therapy in critical patients should not aim at a glucose goal less than 140 mg/dL (American Diabetes Association suggests a 140–180 mg/dl range). However, there are no guidelines for treating hyperglycemia in patients after pancreatic surgery, specifically taking into account the increased risk of hypoglycemia due to impaired counterregulation [116]. Intensive subcutaneous insulin therapy using a sliding scale approach is unpractical, especially in the first few days after surgery when the patient is still not eating. On the other hand, protocols for continuous intravenous insulin infusion have not been tested in patients with total pancreatectomy, in whom the expected rate of hypoglycemia is likely to be higher than observed in the NICE-SUGAR study (6.8 %) [117]. The postoperative use of an artificial endocrine pancreas with a closed loop system (target blood glucose 80–110 mg/dl) has recently been shown to be effective in controlling blood glucose levels, while minimizing the occurrence of hypoglycemia [118, 119••]. However, testing of such a system in "real-world conditions" is not yet available.
2. Referral to a diabetes education program of patients with diabetes following total pancreatectomy

   Due to the "brittleness" of diabetes after total pancreatectomy, patient education and self-monitoring are crucial. Insulin therapy is mandatory in these patients and, generally, overnight insulin requirement is lower than in T1D, while postprandial requirement can be higher. The classic basal bolus regimen with long-acting and short-acting insulin analogues can be used, even if specific studies on this topic are not reported in the literature. In well-motivated and educated patients, insulin treatment by continuous subcutaneous infusion (external insulin pumps) may be used to achieve and maintain good metabolic control. The use of continuous glucose monitoring (CGM) [120] should be considered in patients with frequent life-threatening severe hypoglycemia during follow-up. There are no data available on the concomitant use of insulin with oral agents in these patients. At least from a speculative point of view, metformin should be avoided because even if it slows hepatic gluconeogenesis, it increases the glycolysis in peripheral tissues, which is not desirable in cases with frequent hypoglycemia. The glycemic target in these patients should be planned taking in consideration age, comorbid conditions (i.e., cancer, alcohol abuse, etc.…), life expectancy and a relatively low risk of macrovascular complication. Independently by the regimen, preventing hypoglycemia is a priority in these patients: no skipping meals; frequent small meals; frequent capillary glucose measurements, especially during and after physical activity; no alcohol intake; and mandatory capillary glucose measurements prior to

driving a vehicle and during long drives. In case of hypoglycemia, patients need to be trained to treat it aggressively and patients should keep glucagon for intramuscular injection with them at all time, family members and coworkers need to be instructed about signs and symptoms of hypoglycemia, how to help the patient correcting low blood glucose values, including how to use glucagon in case of severe hypoglycemia.

3. Screening for diabetes following partial pancreatectomy

After pancreatic resection, 20–50 % of patients will develop diabetes [121]. There are limited data available to guide in predicting which patients will develop diabetes postsurgery. We recently reported in a prospective cohort of 651 patients that older age, higher fasting glycemia, higher weight/BMI, higher HOMA2-IR at the presurgery evaluation, and diagnosis of pancreatic malignant disease were all associated with new onset diabetes after surgery for pancreatic disease [29•]. Moreover, presurgery glycated hemoglobin (HbA1c), diagnosis of chronic pancreatitis, and distal pancreatectomy are associated with the development of diabetes after surgery [122, 123]. On the basis of these evidences, all patients should be educated on how to recognize signs and symptoms of hyperglycemia, and/or routine screening for diabetes should be considered at 3 months and 1 year after surgery and every year thereafter, through the measurement of fasting glucose and/or HbA1c.

4. Treatment of diabetes after partial pancreatectomy

The agents which are commonly prescribed are the same as for T2D, although no evidence-based recommendations exist since large clinical trials like the UKPDS excluded patients with pancreatic diabetes, and available observational data are inadequate for developing evidence-based guidelines for these patients. Treatment should include efforts to promote lifestyle changes which may improve glycemic control and minimize the risk of hypoglycemia (minimize high glycemic index foods, healthy diet, physical activity, abstinence from alcohol, smoking cessation, etc.). Patients are generally treated with metformin as the drug of first choice. There is not specific rationale for this choice, since in most patients with diabetes following partial pancreatectomy, hyperglycemia is driven by insulinopenia rather than insulin resistance. Because of the risk of lactic acidosis, metformin should be avoided in patients with ongoing alcohol abuse. As for the prescription of other oral agents for the treatment of diabetes,

(a) Sulfonylureas are associated with an increased risk of severe and prolonged hypoglycemia and should not be prescribed.
(b) Glinides are also associated with an increased risk of hypoglycemia; however, their half-life is much shorter than that of sulfonylureas and glinides at low dose may be considered before switching the patient to insulin therapy.
(c) Alpha-glycosidase inhibitors can aggravate the existing exocrine insufficiency and, therefore, should not be prescribed.
(d) Incretin-based therapy may be associated with an increased risk of pancreatitis and should not be prescribed until safety is proven in these patients.

Most patients do not respond satisfactorily to oral agents and should be switched to insulin treatment, with twice daily pre-mixed insulin or multiple daily injections. Even if lipid-lowering therapy and antihypertensive drugs are less often prescribed to patients with pancreatic diabetes than to T1D/T2D patients, it seems appropriate to offer these patients the same vigorous cardiovascular risk factor intervention as other patients with diabetes.

5. Monitoring nutritional status and preventing malnutrition

Because of the lack of exocrine pancreatic enzymes, patients are likely to develop malnutrition-related problems. Adequate pancreatic enzyme replacement therapy should be instituted early on to prevent qualitative malnutrition and metabolic complications. Malnutrition may also affect glucose management, increasing the susceptibility of patients to swings in glucose levels.

Diabetes After Pancreatic Surgery: Treatment with Islet Autotransplantation

The first autologous transplant of endocrine pancreatic islets was performed at the University of Minnesota in 1977 [124]. It was initially developed for patients with chronic pancreatitis for whom total pancreatectomy was indicated as the best option to relieve pain but who would then develop insulin-dependent diabetes. Since then, more than 500 autotransplantations of islets in patients with near-total or total pancreatectomy for chronic pancreatitis have been performed [125]. The University of Minnesota has published the largest series [126, 127••, 128, 129], and they have described that overall, one third of their patients achieve insulin independence, and the majority have islet graft function, as documented by a positive fasting C-peptide [127••, 130]. Investigators from Cincinnati [131, 132], Leicester [130, 133–136], and other centers have published similar results [137, 138]. The most important factor associated with the rate of insulin independence is the number of islet cells transplanted per kilogram of patient's body weight: different studies have considered a number of islet equivalent per kilogram >2000 [129], > 3000 [134], or >5000 [139] as capable of restoring insulin

independence. Studies show that up to 82 % of recipients maintain glycated hemoglobin <7 % [127••].

The ideal patients for the autotransplantation of islets are those who suffer from chronic pancreatitis with severe pain uncontrolled by pain medications alone and very poor quality of life, had chronic pancreatitis on imaging, and adequate islet cell function prior to surgery ("Minnesota criteria") [140].

Table 2 Indications for IAT according to the Milan Protocol

I. Clinical indications for IAT (must have either of the following)

A. Pancreatitis

Chronic pancreatitis: in cases of non-dilated duct without any cephalic mass when subtotal or total pancreatectomy is indicated (refractory pain in patients in whom medical therapy has failed)

Acute pancreatitis: in cases of relapsing disease (≥3 episodes over 6 month without evidence of current gallstone or other correctible etiology)

B. High-risk pancreatic stump

Patients undergoing pancreaticoduodenectomy in whom pancreatic anastomosis was deemed at high risk for leakage (according to the judgment of the chief surgeon), based on a combination of narrow duct and soft and/or frail pancreatic texture (NCT01346098)

C. Extensive distal pancreatectomy

For benign/borderline neoplasm located at the pancreatic body neck (as an alternative to median pancreatectomy)

D. Severe complications after pancreatic surgery

Grade C pancreatic fistula, according to the definition of the International Study Group on Pancreatic Fistula, requiring relaparotomy with completion pancreatectomy or left pancreatectomy

II. General indications for IAT (must have each of the following, 1–4)

1. Patient age >18 year
2. Fasting glycemia <126 mg/dL without glucose-lowering medications
3. Ability to provide written informed consent
4. Mental stability and ability to comply with study procedures

Contraindications

The presence of a pancreatic malignant disease was not an exclusion criterion per se, whereas patients who met any of the following criteria were not eligible:

1. Presence of any multifocal pancreatic neoplasm at preoperative imaging or intraoperative evaluation
2. Diagnosis of IPMN, unless the absence of multifocal lesion is demonstrated by endoscopic ultrasound
3. Involvement of the pathologic pancreatic transection margin, including any degree of dysplasia or ductal disepithelization. If a malignant disease is the reason for the surgery, 1 cm of the pancreatic remnant close to the pancreatic margin will be resected and sent for immediate pathologic analysis to confirm margin negativity and to rule out multifocal tumor.
4. Diagnosis (suspected or ascertained) of multiple endocrine neoplasm
5. Any medical condition that, in the opinion of the investigator, might interfere with the safe completion of IAT

Balzano G, Piemonti L. Autologous islet transplantation in patients requiring pancreatectomy for neoplasm. Curr Diab Rep. 2014; 14:512 [28•]

Patients with hereditary pancreatitis, such as those with cystic fibrosis, are accepted in autotransplant programs, whereas patients with pancreatic malignancy have been excluded, at least up until recently. The exclusion is dictated by the perception that pancreatic malignancy is a potentially multifocal cancer. Given that it is impossible to completely purify pancreatic islets, autotransplant may cause the infusion of malignant cells into the patient during the transplant. We recently suggested the possibility to extend islet autotransplantation to patients with known malignancy, either having completion pancreatectomy as treatment for severe pancreatic fistulae or extensive distal pancreatectomy for benign/borderline neoplasms of the pancreatic neck (as an alternative to central pancreatectomy) or pancreatoduodenectomy because at high risk of pancreatic fistula (i.e., presence of a narrow pancreatic duct and soft residual parenchyma) [29•, 141••] (see Table 2).

Conclusions

A growing number of patients with total or partial pancreatectomy and long life expectancy are exposed to the risk of hyperglycemia, with a significant impact on quality and duration of life. Clinically, this type of diabetes presenting as a feature of generalized pancreatic insufficiency is difficult to control, but there is a remarkable paucity of recently published studies and there is no consensus regarding treatment pathways. We can conclude that the clinical management is mainly based on center experience and includes a trial of oral hypoglycemic drug and insulin if there is inadequate response. In selected cases, islet autotransplantation can be considered to improve postoperative glycemic control. Referral centers for pancreatic surgery should collaborate closely with diabetes specialists and islet isolation facilities to provide the best care to patients after pancreatic surgery.

Acknowledgments This study was supported by the Associazione Italiana per la Ricerca sul Cancro (AIRC, bando 5×1000 N_12182 and Progetto IGN_ 11783).

Compliance with Ethics Guidelines

Conflict of Interest Marina Scavini reports personal fees and non-financial support from Roche Diagnostics.

Erica Dugnani, Valentina Pasquale, Daniela Liberati, Francesca Aleotti, Gaetano Di Terlizzi, Giovanna Petrella, Gianpaolo Balzano, and Lorenzo Piemonti 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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- • Of importance
- •• Of major importance

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