

Review

Endocrine and Metabolic Insights from Pancreatic Surgery

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Although it is well established that diabetes can also develop as a result of diseases or maneuvers on the exocrine pancreas, the complex relationship between glucose disorders and underlying pancreatic disease is still debated. There is evidence that several features linked to pancreatic diseases can modify endocrine and metabolic conditions before and after surgery. However, pancreatic surgery provides a rare opportunity to correlate *in vivo* endocrine and metabolic pathways with *ex vivo* pancreatic samples, to examine the endocrine and metabolic effects of acute islet removal, and finally to clarify the pathogenesis of diabetes. This approach could therefore represent a unique method to shed light on the molecular mechanisms, predicting factors, and metabolic consequences of insulin resistance, islet plasticity, β cell failure, and type 2 diabetes.

Introduction

Diabetes mellitus is a cluster of conditions characterized by persistent hyperglycemia caused by quantitatively and/or qualitatively insufficient secretion of insulin – triggered by a combination of metabolic, autoimmune, genetic, environmental, and exocrine pancreas factors [1]. The most prevalent form, type 2 diabetes, has an intricate pathogenesis that is characterized by impaired insulin sensitivity associated with an inadequate compensatory insulin response. However, diabetes can also develop as a consequence of diseases or maneuvers on the exocrine pancreas, such as pancreatic surgery. Although pancreatic surgical procedures are generally standardized, diabetes occurrence seems to depend on nonsurgical patient characteristics. As in any other form of diabetes, the occurrence of hyperglycemia is a consequence of the amount of insulin necessary to maintain euglycemia (i.e., insulin resistance) and the characteristics (quantity and quality) of the remaining insulin-secreting cells together with glucagon, are responsible for dysregulation of glucose metabolism. While exploring *in vivo* the relative contributions of insulin resistance and insulin secretion to the regulation of glucose metabolism before and after surgery, we had the rare opportunity to examine *ex vivo* specimens from the same patients who had undergone accurate metabolic and hormonal profiling.

With this method, we adopted a new approach to explaining the seemingly contradictory results from different cross-sectional studies investigating the role of pancreatic surgery in determining diabetes [2]. Further, we explored islet cell biology in a new pathophysiological manner, looking for *in vivo* and *ex vivo* correlations [3]. Finally, pancreatic surgery is a model for determining the role of the sole (acute) β cell mass reduction, allowing insights into signaling pathways in human islet cells and the specific molecular features which determine β cell failure in type 2 diabetes.

In this review we aim to clarify the endocrine and metabolic implications of pancreatic surgery and surgically treated pancreatic disorders, and how they are related to the appearance of diabetes.

Highlights

Pancreatic disease can modify endocrine and metabolic homeostasis; however, islet characteristics play a major role in the possible appearance of diabetes.

Partial pancreatectomy is an ‘accelerator’ of declining β cell function rather than the actual cause of diabetes. That is, diabetes appearing after partial pancreatectomy could be better classified as ‘accelerated’ type 2 diabetes rather than as type 3c.

Pancreaticoduodenectomy requires, for anatomical reasons, the removal of ‘healthy’ tissue from which accurate *ex vivo* specimens can be obtained.

Pancreatic surgery provides a rare opportunity to correlate *in vivo* endocrine and metabolic pathways (before surgery) with *ex vivo* data from pancreatic samples.

Pancreatic surgery is an excellent model for examining the metabolic and hormonal effects of acute islet removal.

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Advantages of Studying Patients Electing for Partial Pancreatectomy

Robust findings in murine and *in vitro* models, reviewed by Migliorini *et al.* [4], reveal that endocrine and exocrine cell types within the pancreas preserve a level of cellular plasticity, with obvious important consequences for diabetes pathophysiology; however, the transferability of murine experiments to humans remains controversial. Furthermore, the major challenge in investigating human islet biology is the lack of accurate *in vivo* metabolic and hormonal profiling of the subjects studied coupled with tissue samples of appropriate quality for analysis. Moreover, because islet morphology and cellular composition may vary throughout the pancreas [5], the reproducibility and reliability of results depend on the location of the pancreas samples obtained by the rigorous surgical procedure described above.

Direct evidence in the context of human islet morphology also remains limited by the lack of mirroring between pancreas morphology and function (reviewed by Mezza *et al.* [2]). Most studies on human pancreas biology have evaluated autopsy pancreata or organs from donors [2], where the mandatory time-lag between death and sampling from autopsy (usually >24 h), as well as the severe medical conditions of organ donors before pancreas explant, could certainly limit the morphological quality of the samples and alter the transcriptomic signature [6–8]. In addition to the variable morphology and molecular pathways, a lack of detailed medical history and metabolic profiling often precludes accurate classification of donors as ‘controls’ (usually simply ‘nondiabetic’, but with undefined changes in insulin secretion and glucose metabolism) and subclassification of patients with diabetes. Indeed, studies in which pancreatic samples were collected during surgery for morphological studies in individuals with normal glucose tolerance, as established by oral glucose tolerance testing (OGTT), and subclassified on the basis of insulin sensitivity, indicate that islet remodeling represents a continuous process during the transition from ‘normal, insulin-sensitive’ to ‘prediabetic, insulin-resistant’ even in the absence of overt diabetes [2]. Only a point-to-point link between *ex vivo* morphology of islets – collected from the same pancreatic region in all patients – and *in vivo* functional markers of islet secretion – collected with state-of-the-art methods – can provide a clear explanation of how molecular and morphologic changes influence islet behavior *in vivo*.

Furthermore, accurate metabolic profiling requires sensitive, specific, and proven *in vivo* tools. Thus, for patients whose pancreatic samples are to be analyzed *ex vivo*, a combination of OGTT, hyperinsulinemic–euglycemic clamp and hyperglycemic clamp procedures, and mixed-meal test, performed using standard procedures as previously reported [9–11], can be considered to be the state-of-the-art technique for a full description of the hormonal and metabolic features of the patients [12].

A consistent body of evidence has shown that insulin resistance drives the early compensatory phase in the natural history of type 2 diabetes, remodeling islet cell morphology by increasing the amount of islet cells in attempting to cope with increasing insulin demand, but also generating β cell dysfunction, even during the euglycemic compensatory phase [12]. The hyperinsulinemic–euglycemic clamp test, first described by DeFronzo and colleagues [10], represents the gold standard for measuring whole-body peripheral insulin sensitivity, and has been used to characterize candidates for partial pancreatectomy [12,13]. Owing to lack of a clear consensus regarding the cut-off for insulin resistance, we employed the median value of glucose uptake among the study cohort: subjects whose glucose uptake was above the median value were classified as ‘more insulin-sensitive’, and subjects whose glucose uptake was below the median were defined as ‘more insulin-resistant’. Subsequently, an in-depth phenotyping of the insulin secretion pattern was conducted by means of a hyperglycemic clamp, in which, through infusion of intravenous glucose, plasma glucose is clamped at a stable level of 125 mg/dl above the

fasting blood glucose concentration, and a series of 15 samples are collected over 2.5 h. Using this procedure, which is often supplemented with an arginine infusion, it is possible to distinguish the first phase of insulin release, reflecting the early insulin peak secreted from pancreatic β cells in response to glucose stimulation (first 10 minutes of the clamp), the second-phase insulin release, reflecting β cell function under sustained elevated glucose levels (between minutes 10 and 120), and β cell secretory capacity calculated as the insulin response during the 30 minutes following a 5 g arginine bolus, which reflects the maximum insulin secretory capacity at a steady-state blood glucose concentration. To further characterize the relationship between insulin resistance and changes in β cell function and islet morphology, β cell function can be estimated as insulin secretion rate derived from C-peptide levels by deconvolution [14] during OGTT, mixed-meal test, or hyperglycemic clamp. β -Cell glucose sensitivity (β CGS), namely the slope of the relationship between insulin secretion and glucose concentration, can also be estimated from the mixed-meal, oral glucose, and hyperglycemic clamp tests by modeling, as previously described [15,16].

All these *in vivo* functional markers of islet cell function, coupled with *ex vivo* analysis of islets, represent a unique option to study diabetes pathophysiology.

Metabolic Effects of Partial Pancreatectomy: Evidence So Far

The incidence of diabetes after pancreatic surgery varies with different surgical procedures and the underlying etiology of the disease requiring surgery (Box 1). The distribution of the hormone-producing cells in the pancreas is one of the main prognostic factors in the incidence of new or worsening of existing hyperglycemia that can occur after pancreatic surgery. Evidence in humans shows that insulin-producing β cells are distributed evenly throughout the pancreas, as are cellular composition and islet architecture, with no regional differences in glucose-stimulated insulin secretion in islets isolated from different portions of the pancreas. However, islet density and distribution have recently been suggested to be twofold higher in the tail region than in the head and body region [5]. This suggests that distal pancreatectomy could have a different impact on glucose metabolism compared with resection of the head region. Regardless of the extent and region of pancreas removal, it has also been shown that various intraoperative techniques used to manage the pancreatic remnant, aiming to reduce the risk of the dreaded complications related to pancreatic anastomosis [17], have an impact on residual β cell function and diabetes risk [18]. As an example, pancreatic duct occlusion with different types of glue during pancreatectomy has led to a marked reduction in mortality, but has been criticized for causing major impairment of the endocrine function of the pancreas [19].

Several animal models of pancreas ablation, for example streptozotocin-administered baboons [20] and variable pancreatectomy in rats [21–23], have shown a lower rate of development of diabetes than expected, suggesting that β cell regeneration and/or the appearance of new small islets could compensate for decreasing β cell mass. It has also been shown that a 50% pancreatectomy of distal pancreas in healthy donors induces impaired glucose tolerance in only 25% of patients [24]; diabetes does not seem to develop unless 60% or more of the gland is removed [25–27]. However, long-term results of distal pancreatectomy for chronic pancreatitis in 90 patients also showed a 46% risk of diabetes over 2 years. The extent of pancreatectomy is significantly associated with the development of diabetes. Splenic conservation was associated with reduced incidence of postoperative diabetes in pancreatectomy, with rates varying from 34% to 75% [26].

By contrast, the reported postoperative diabetes rate after pancreaticoduodenectomy performed according to Whipple's procedure, in which pancreatic mass is reduced by ~50%, is about 10–

Box 1. Pancreaticoduodenectomy Techniques

Pancreatic surgery is indicated for the treatment of chronic pancreatitis complications (intractable pain, biliary obstruction, duodenal stenosis, pancreatic duct stenosis, pseudocysts, pancreatic ascites, portal venous compression from splenic/mesenteric venous thrombosis, pancreatic hemorrhage, and others) and for the resection of pancreatic or periampullary tumors. All surgical interventions aim to preserve as much of the functioning pancreatic parenchyma as possible because metabolic abnormalities subsequent to pancreatic resection apparently depend on the part (head versus tail) of the pancreas and the percentage of the gland removed [86], as well as on the specific surgery performed.

Pancreaticoduodenectomy, also called Whipple's surgery, is a complex procedure that is commonly used to remove malignant as well as benign tumors including pancreatic head cancers, periampullary tumors or tumors of the distal portion of the common bile duct, benign intraductal papillary mucinous neoplasms [86–88], mucinous cystic neoplasms, and neuroendocrine tumors. Moreover, it has also recently been proposed for the treatment of painful chronic pancreatitis [89,90].

This surgical technique was first described by Whipple in 1935 [91,92] as a single-stage removal of the distal part of the stomach, the pancreas head, the first part of the small intestine (duodenum and first portion of the jejunum), the gallbladder, and the bile duct. In 1972, Traverso and Longmire proposed a modification of the conventional procedure, the pylorus-preserving pancreaticoduodenectomy technique, in which the duodenum is cut about 2–3 cm below the pylorus: this results in a significant decrease in the incidence of postoperative dumping, marginal ulceration, and bile reflux gastritis [93]. At the end of the procedure, continuity of the pancreatic, biliary, and gastrointestinal tract systems is reestablished through pancreaticojejunostomy between the pancreatic stump or the main pancreatic duct and the small intestine [87,94].

The main advantage of using this operation as a source of pancreas samples and as a model of acute islet mass reduction is the reproducibility of the technique. In particular, the removal of the pancreas head from the body-tail region requires a surgical cut which comprises four main features of pancreatic segmentation: anatomic, embryologic, vascular, and lymphatic. Anatomically, the pancreas is divided into four macroscopic regions (head, isthmus, body, and tail), but there is no distinct line that delimits these portions and this segmentation remains virtual, therefore unusual in surgical practice [95]. Another point of view considers the embryonic development of the pancreas as a guide to pancreatic surgical segmentation and pancreatic head resection [96]. The pancreas arises from the fusion of two buds from the foregut: the dorsal pancreatic bud forms the neck, body, and tail of the developed pancreas, and after rotation the ventral pancreatic bud forms the head and the uncinate process [97]. Given this separate origin and the lack of a specific lymphatic drainage [98], some reports consider the fusion plane between the two buds as a cleavage point for division of the organ during surgical procedures [99]. In the human pancreas, the isthmus roughly separates the right and the left pancreas, thus representing the section site for pancreaticoduodenectomy [100]. These two portions each depend on a different major arterial system, the gastroduodenal and the splenic arteries, respectively, which could thus be assimilated to vascular domains. Thus, pancreatic vascularization can guide resection during surgery. In fact, a crucial step during pancreaticoduodenectomy is the isolation of the mesenteric artery [101]. The surgeon can cut the pancreas along the venous plane, dissecting the uncinate process and the head of the pancreas from surrounding tissues only after this procedure. The lymphatic system and mesopancreas, a layer covering the dorsal part of the pancreas up to the mesenteric vessels, have also been mentioned by Gockel *et al.* [102] as important features to consider in pancreas resection and, especially in the presence of pancreatic tumors, to avoid cancer diffusion along the peripancreatic neural plexuses.

The volume of pancreas removed during the surgery is virtually constant (~50%), as previously reported by Schrader *et al.* [39], and the strict surgical procedure to resect the pancreas ensures that samples collected come from the same pancreatic region. Thus, for vascular reasons, pancreaticoduodenectomy is always performed with the same technique, and pancreas samples collected at the edge of the surgical cut always derive from the same area. The latter is also the main site of β cell loss in type 2 diabetes [5]. This is a major advantage for the reproducibility of *ex vivo* and post-surgery experiments.

25%. In a randomized prospective trial of 20 patients, Buchler *et al.* [28,29] showed better glucose tolerance in patients whose duodenum was preserved compared with others.

Several interesting studies suggest that a reduction in β cell mass may also reduce glucose disposal in peripheral tissues. In the dogs studied by Matveyenko *et al.* [30], 50% pancreatectomy resulted in impaired fasting glucose or impaired glucose tolerance, a reduction in the pulse mass of glucose-induced insulin secretion, a decrease in hepatic insulin extraction, and a 40% reduction in insulin-stimulated glucose disposal. These findings raise the provocative possibility that β cell mass reduction may not only have effects on insulin secretion but may also

play a role in impaired insulin action, although the latter could simply be the consequence of prevailing hyperglycemia and glucose toxicity [31]. Conversely, in humans, insulin sensitivity did not change significantly after surgery [12,32], suggesting that the removal of underlying disease and the β cell mass reduction does not improve insulin action.

As expected, evaluation of glucose homeostasis by standard OGTT (75 g) in a cohort of individuals who underwent pancreaticoduodenectomy revealed a worsening of glucose tolerance after surgery [12,33]. Furthermore, evaluation of insulin secretion by a hyperglycemic clamp over 2 h, followed by acute stimulation with L-arginine, demonstrated significant reduction after surgery, with an even greater (76%) reduction of insulin secretion in response to arginine. In a recent study, we showed that the increase in the proinsulin to insulin ratio after physiological stimulation of insulin secretion is further amplified following acute β cell mass reduction, indicating a significant impairment of proinsulin processing, possibly due to increased β cell workload and endoplasmic reticulum stress [13] (Table 1).

An additional factor that impacts on glucose tolerance after pancreaticoduodenectomy is the change in incretin secretion that is mainly caused by removal and anastomosis of gut segments following pancreaticoduodenectomy. Indeed, a predictable consequence of this surgery is a marked decrease in gastric inhibitory polypeptide (GIP) secretion [34], presumably a direct consequence of the duodenectomy and bypass of the most proximal small intestine. The operation is also associated with increased secretion of glucagon-like peptide 1 (GLP-1), which reached levels comparable with those observed after gastric bypass surgery [35]. This raises the possibility that bypassing the duodenum/proximal jejunum has beneficial metabolic effects; these may be related to the increased secretion of GLP-1 in the gut but could also be due to the lack of secretion of the hypothesized duodenal diabetogenic factor [36] and/or to intra-islet GLP-1 production [2], although this is a controversial issue.

Increased circulating GLP-1 levels enhance glucose-stimulated insulin secretion, and might have a beneficial effect on glucose metabolism following surgery [37], but do not inhibit glucagon release – as expected in view of its glucagonostatic effects [38]; on the contrary, glucagon levels increased significantly after this operation [12]. Reduced systemic insulin levels may have contributed to the exaggerated glucagon responses [39], but the possibility that the gut is actually the source of the increased glucagon levels cannot be excluded [40].

To further evaluate changes in glucose tolerance after removal of 50% of the pancreas, we compared 'more insulin-resistant' and 'more insulin-sensitive' (as described earlier) nondiabetic individuals before surgery. Despite the removal of the same amount and region of pancreas, patients identified as insulin-sensitive preserved their glucose tolerance, whereas 77.7% of insulin-resistant patients developed diabetes, as confirmed by 75 g OGTT and glycated hemoglobin (HbA1c) >7%. In addition, insulin resistance directly impacted on proinsulin processing, leading to increased relative proinsulin release, detectable only in the presence of increased insulin secretion demand, as a result of acute β cell mass reduction [14]. In addition, our group studied pancreatic samples from the same cohort of nondiabetic individuals [13,16], and found a 50% greater fractional β cell area and islet size in insulin-resistant subjects compared with insulin-sensitive controls. Of note, *in vivo* β cell dysfunction has been correlated to alterations in islet dimensions and islet architecture, suggesting that the β cells themselves emit signals to induce their own potential mechanisms of compensation [16]. However, only patients with previous insulin resistance, who already have islet remodeling and impaired β cell function, develop diabetes after surgery. This suggests that acute removal of β cell mass inevitably accelerates a decline in β cell functional capacity, which was already previously 'stressed' in

Table 1. Baseline Clinical Characteristics and Metabolic Effects of Surgery in Studies Recruiting Candidates for Pancreaticoduodenectomy (PD)^a

Metabolic study	Study population before PD		Metabolic effect after PD compared with baseline					
	Glucose metabolism	Pancreatic disease	Insulin resistance	Insulin secretion	Glucose levels	% Diabetes	GLP-1, glucagon, and GIP levels	Proinsulin/insulin ratio
Menge <i>et al.</i> [32]	Nondiabetic (HbA1c >5.7%)	Chronic pancreatitis, pancreatic cancer, or with extra-pancreatic or benign pancreatic tumor	No changes (Matsuda index)	50% reduction after OGTT (75 g)	Transient reduction immediately after OGTT (75 g)			
Litwin <i>et al.</i> [33]	Non-diabetic	Chronic pancreatitis		Reduction after OGTT (75 g)	Increased after OGTT (75 g)	29% at 2 months and 43% at 6 months		
Pannala <i>et al.</i> [52]	Longstanding diabetic (FPG >126 mg/dl or antidiabetic treatment and >2 year duration)	Pancreatic cancer			Reduction of mean FPG	100% at 2 months; 91% at 8 months		
	New-onset diabetic (FPG >126 mg/dl or antidiabetic treatment and <2 year duration)	Pancreatic cancer			Reduction of mean FPG	43% at 2 months; 47% at 8 months		
	Nondiabetic (NFG, FPG <99 mg/dl; IFG, FPG 100–125 mg/dl)	Pancreatic cancer			Reduction of mean FPG	~15% at 2 months		
Kang <i>et al.</i> [54]	Diabetic (HbA1c 6.5%, FPG >126 mg/dl, or 2 h glucose OGTT >200 mg/dl)	Pancreatic cancer (45.6%) and other pancreatic disease (54.4%)	Decreased (HOMA-IR)	Reduced fasting insulin and c-peptide levels	Reduced fasting and 2 h after OGTT (75 g)	59.6% at 12 months		
Mezza <i>et al.</i> [12,13]	Nondiabetic (HbA1c <5.7%)	Tumor of the ampulla of Vater	No changes (hyperinsulinic-euglycemic clamp)	76% reduction of arginine-stimulated insulin secretion after glucose infusion	Increased after OGTT (75 g)	38% at 2 months	GLP-1 and glucagon: increased after MMT GIP: reduced after MMT	Increased over 4 h MMT
Mezza <i>et al.</i> 2018 [13]	IR versus IS	Tumor of the ampulla of Vater	No changes (hyperinsulinic-euglycemic clamp)	Greater reduction of all phases of insulin secretion after HC compared with IS	Greater increase after OGTT (75 g)	77.7% at 2 months versus 0% at 2 months	Glucagon increased after MMT compared with IS	Different and opposite effects on time-dependent changes (P/I increased only in IR)

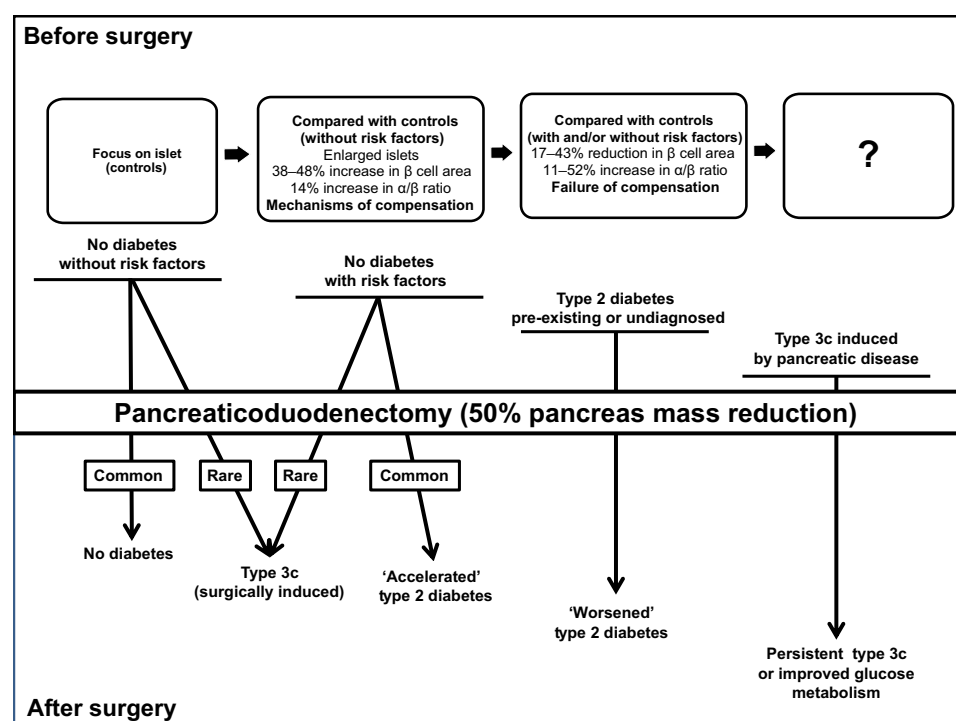
^aAbbreviations: FPG, fasting plasma glucose; GIP, gastric inhibitory peptide; GLP-1, glucagon-like peptide 1; HC, hyperglycemic clamp; HOMA-IR, homeostatic model assessment of insulin resistance; IFG, impaired fasting glucose; IR, insulin-resistant; IS, insulin-sensitive; MMT, mixed-meal test; NFG, normal fasting glucose; OGTT, oral glucose tolerance test.

the attempt to compensate for increasing insulin demand [2]. Because the surgical procedure is the same in all subjects, but only patients with previous islet remodeling and impaired β cell function develop hyperglycemia and diabetes, the true determinant of the appearance of diabetes is the pre-existing 'pre-diabetic' milieu rather than the surgery. Therefore, except in rare cases, these patients should be classified as having 'surgically accelerated' type 2 diabetes rather than secondary, type 3c diabetes (Figure 1).

Controversial Relationship between Pancreatic Cancer and Diabetes

Several studies support an association between diabetes and pancreatic cancer, but this 'chicken and egg' conundrum remains unresolved [41,42]. It has been reported that 80% of pancreatic cancer patients, at time of diagnosis, have either impaired glucose tolerance or diabetes [43,44]. Conversely, epidemiological studies describe an increased incidence of pancreatic cancer in diabetic populations, with a relative risk that ranges from 1.5 to 2.0 [45].

These observations have led to a debate as to whether pancreatic cancer causes diabetes or whether diabetes is a risk factor for the development of pancreatic cancer [42,46–48]. Ductal adenocarcinoma is the most common type of exocrine tumor of the pancreas, and by 2030 it



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Figure 1. Spectrum of Glucose Metabolism States before Pancreaticoduodenectomy and Potential Evolution after Surgery. Nondiabetic individuals without risk factors for type 2 diabetes (obesity, insulin resistance, family history, impaired fasting glucose, impaired glucose tolerance) commonly preserve normal glucose metabolism after surgery, and they rarely develop surgically induced type 3c diabetes following acute β cell mass reduction. Altered islet structure and active mechanisms of compensation before surgery lead to 'accelerated' type 2 diabetes or surgically induced type 3c diabetes in nondiabetic individuals with risk factors. Impaired glucose metabolism worsens after surgery in type 2 diabetic individuals with reduced β cell mass and failure of compensation capacity. Type 3c diabetes induced by primary pancreatic disease can persist after surgery or even improve depending on the type, duration, and features linked to underlying disease. No data are available on changes of islet structure in type 3c diabetes induced by primary pancreatic disease, and it can be challenging to distinguish new-onset or undiagnosed type 2 diabetes from some type 3c cases.

is projected to become the second leading cause of adult cancer mortality [49]. Symptoms usually do not appear until the disease is advanced, with a consequent extremely low survival rate (overall 5 year survival rate of 7–8%) [50]. Of note, 1% of pancreatic cancer patients receive a diabetes diagnosis 24–36 months before the diagnosis of pancreatic cancer, when the tumor is still radiographically occult, representing a potential alarm signal for early diagnosis of pancreatic cancer [51,52].

The prevalence of diabetes in pancreatic cancer ranged between 4% and 23% in epidemiological studies using self-report or review of medical records or death certificates to identify physician-diagnosed diabetes [53]. In a prospective study of 512 cases of pancreatic cancer and 933 controls, nearly half the cases met the criteria for diabetes, which was frequently new-onset (<2 year duration); interestingly, diabetes diagnosis was associated with conventional risk factors for type 2 diabetes (such as age, body mass index, and family history of type 2 diabetes), but not with tumor stage or location. A 57% resolution of these new-onset diabetes cases has been reported after tumor resection, whereas longstanding diabetes persists, suggesting that direct interference with insulin secretion or action is induced by the malignancy [52,54]. Partial pancreatectomy, however, is usually followed by several metabolic changes, including significant weight loss, which in turn might have indirectly ‘cured’ newly diagnosed diabetes. Despite the role of both peripheral insulin resistance and islet dysfunction observed in these patients, it is important to note that metabolic information was self-reported and that diabetes diagnosis was based only on fasting plasma glucose levels >126 mg/dl, and a more accurate metabolic evaluation is recommended to exclude a previous diagnosis and confirm diabetes remission after surgery. Insulin resistance has been described in pancreatic cancer patients [43,55–57], with an improvement 3 months after tumor resection. Several studies (Table 1) have attempted to identify the mechanisms underlying peripheral insulin resistance in pancreatic cancer, and some data suggest that the cancer may impair the insulin signaling cascade at multiple points, either directly (e.g., a post-insulin receptor defect induced by substances released by cancer cells, which impairs skeletal muscle glycogen synthesis and glycogen storage [58]), or indirectly (by the proinflammatory tumor microenvironment which accompanies the disease [59]).

Furthermore, an inadequate β cell response to stimuli that progresses to β cell failure has also been described [60]. In fact, *in vivo* human studies suggest that the altered bile flow occurring after obstructive jaundice caused by extrapancreatic tumor obstruction may impair β cell secretory functions as a consequence of an altered β cell response to incretin stimulation [61]. Underlying this defect there could be an ultrastructural β cell alteration, which has been described in an experimental model of jaundice, where β cells showed features of immature granules in their cytoplasm [62], and which worsens chronic cholestatic injury [63].

Altered β cell function, as reported in insulin resistance, may also be due to a direct effect of pancreatic cancer products. For example, *in vitro* studies report that the supernatant from a cultured pancreatic ductal adenocarcinoma cell line could inhibit insulin secretion. This effect might be attributable to adrenomedullin, a multifunctional vasoactive peptide that has been implicated in inflammation and sepsis, as well as being highly overexpressed in the pancreatic ductal adenocarcinoma cell, to the extent that it has been proposed as a pancreatic carcinoma biomarker [64,65]. Other candidate biomarkers are currently being validated, for example neuromedin U, a peptide overexpressed in pancreatic cancer which can induce insulin resistance and alter β cell function [66,67]. In addition, Hart *et al.* [68] suggested a deficiency in pancreatic polypeptide (PP) release in response to meals as a potential marker of cancer of the head of the pancreas, but further investigations will be necessary to determine whether this observation

is clinically useful as a screening tool for detecting pancreatic cancer in new-onset diabetes patients.

In addition to altered β cell function, morphological abnormalities of the endocrine pancreas in proximity to the pancreatic carcinoma have also been described [69]. In 70% of pancreatic cancer patients, pancreatic islet cells were positive for ductal cell markers, and this was associated with reduced insulin content and increased glucagon expression. Moreover, an abnormal colocalization of islet hormones has also been described [69–72]. In light of the above data, studies have suggested that diabetes is caused by the tumor rather than being only a risk factor [56,73–75].

However, as mentioned, epidemiological studies report a relative risk of developing pancreatic cancer that ranges from 1.5 to 2.0 in longstanding diabetes, and even propose adding pancreatic cancer to the list of diabetes complications [45]. Nevertheless, insulin resistance, hyperinsulinemia, and obesity-related proinflammatory status are all risk factors for developing pancreatic cancer. During the prediabetes compensatory phase, the islets increase insulin secretion to cope with insulin resistance, and this extra insulin is also secreted into the intrapancreatic portal circulation. The high levels of islet hormones reach ductal and acinar cells and exert a proxocrine effect [76] on insulin receptors and insulin-like growth factor 1 receptors (IGF-1Rs) that are present on acinar cells and any transformed cells, eventually activating mitogenic and prosurvival signaling. In addition, obesity, that is also responsible for insulin resistance, enhances a proinflammatory microenvironment by the secretion of adipokines [e.g., tumor necrosis factor α , galectin 3, interleukin 6 (IL-6), and IL-1 β], which promote mitogenesis and autophagy, thus contributing to malignant epithelial transformation and pancreatic cancer initiation and progression [59,77,78]. Despite the debate on the cause–effect relationship between diabetes and pancreatic cancer, glucose metabolism abnormalities associated with pancreatic cancer can either improve postoperatively or worsen following surgical procedures [79]. Finally, it cannot be excluded that the relationship might simply be due to reciprocal medicalization: a diagnosis of pancreatic cancer is obviously followed by more intensive medical controls, which in turn might include an otherwise missed diagnosis of diabetes. Similarly, a diagnosis of diabetes in the absence of risk factors could induce physicians to explore the possibility of an otherwise missed diagnosis of pancreatic tumor.

In conclusion, there is no definitive answer to the question of what comes first – diabetes or pancreatic cancer. There is evidence for both sides, and further investigations to provide definite answers are clinically relevant, especially to identify people at higher risk of pancreatic cancer who could benefit from early diagnosis. Although there is no final evidence that pancreatic cancer can cause diabetes (or vice versa), the clinical indication to actively search for pancreatic lesions in patients with diabetes but without risk factors should be maintained.

Hormonal and Molecular Effects of Pancreatic Diseases on Islets

The evidence presented earlier suggests a ‘dual causality’ for diabetes and pancreatic carcinoma in that either longstanding diabetes is a risk factor for the development of carcinoma, or, conversely, that pancreatic carcinoma is a presumed cause of diabetes. Importantly, pancreatic disease remains under-recognized as an underlying etiology, considering that 10% of all diabetes cases could be classified as diabetes type 3c, in which chronic pancreatitis is the most common etiology, affecting 80% of cases [80]. Ewald and Bretzel proposed diagnostic criteria [81] to distinguish type 3c diabetes cases (initially misclassified as type 2) from type 2. Despite these criteria, however, differentiating between type 3c and type 2 diabetes remains challenging and prospective validation is needed.

In a retrospective study by Pelaez-Luna *et al.*, 74% of diabetic patients with pancreatic carcinoma were diagnosed with diabetes up to 24 months before the diagnosis of pancreatic carcinoma, frequently at a time when the tumor was radiologically occult [51]. Several studies have attempted to identify mechanisms or genomic and/or protein markers of diabetes that might be induced by pancreatic carcinoma (reviewed by Andersen *et al.* [48]) and thus provide potential predictive factors for earlier pancreatic carcinoma detection, potentially leading to improvement of therapeutic outcome. Further, the substantial percentage of diabetes remission after tumor removal strongly suggests that new-onset diabetes associated with pancreatic carcinoma may be considered to be a paraneoplastic phenomenon in which one or more factors induced by the malignancy interfere with insulin action, leading to manifest poor glycemic control [48].

Cholestasis-induced diabetes has also been described as a surgically reversible dysregulation of blood glucose that is diagnosed concomitantly with a (peri-) pancreatic tumor, and appears to be secondary to compromised liver function owing to a subsequent increase in insulin resistance [82].

Compelling as these data may seem, several problems remain unsolved in the context of this complex relationship. For example, is there any difference between new-onset diabetes associated with pancreatic carcinoma and other peripancreatic tumors which are candidates for the same surgical procedure? Why is it that not all individuals with pancreatic carcinoma develop diabetes? Most studies in the field have investigated the connection between pancreatic carcinoma and diabetes, but there are no reports describing the incidence of diabetes in extra-pancreatic or benign tumors.

In addition, for the purpose of understanding the pathophysiology of β cell failure in different stages of metabolic control, we wonder whether it really matters whether diabetes onset is accelerated by the presence of a pancreatic disease.

Importantly, findings in islets from organ donors [8] and pancreatectomized patients with type 2 diabetes have shown important differences in transcriptomic signatures in the pancreas of pancreatectomized subjects compared with other pancreas sources and isolation procedures, suggesting that individuals with type 3c diabetes show peculiarities that may be correlated to tumor-linked pathogenesis or a different duration and severity of hyperglycemia. However, comparing differently expressed genes with the transcriptomic signature of pancreatic cancer, no evidence was found for contamination of samples from surgery with cancer cells [83], and, in view of rapid amelioration after pancreas head tumor removal, Ehehalt *et al.* argued that glucose intolerance correlates with altered hepatic function and insulin resistance secondary to bile flow alteration [82], rather than reflecting a direct effect of the tumor on such cells.

Recently, a combined genetic and transcriptomic analysis of human islets obtained from brain-dead organ donors or surgical patients detected expression quantitative trait loci (eQTLs) and shed light onto the gene regulatory mechanisms [84]. This study provides a unique up-to-date analysis of ~300 identified genes linked to type 2 diabetes and associated traits in two different cohorts and using different extraction procedures. However, these genes were highly variable among samples, and *in vitro* and *in vivo* metabolic profiling in living surgical donors and functional analyses will be necessary to definitively prove the role of the genes identified in relation to islet cell biology and type 2 diabetes.

It is important to note that islets include several different cell types, and several recent reports have provided a resource of single-cell transcriptomes from healthy and type 2 diabetic donors,

Box 2. Overcoming Limitations in the Model of Pancreaticoduodenectomy

We believe that the adoption of simple strategies could overcome limitations resulting from the complex relationship between pancreatic disease and diabetes. One such strategy is the more accurate selection of individuals whose metabolic features and pancreas samples are likely not affected by the underlying pancreatic disease. First, pancreatic and peripancreatic lesions, which require removal by pancreaticoduodenectomy, are heterogeneous, and preliminary data support the concept that the mechanisms leading to overt hyperglycemia could differ for the various lesions and stages, suggesting that excluding cases of pancreatic carcinoma and selecting subjects with periampullary tumors could significantly increase the reliability of the results deriving from the proposed model.

Second, metabolic evaluation before surgery should be performed only in patients with normal or normalized cholestasis markers, to exclude the possibility that altered bile flow (commonly observed in peripancreatic lesions) could have caused significant impairment in enteroendocrine gut–pancreatic secretory function.

Third, a better classification of individuals according to their presurgical risk factors for type 2 diabetes, namely family history of diabetes, age, obesity, insulin resistance, and previous evidence of mild alterations of glucose metabolism, could help to clarify cases where the underlying disease has accelerated an already expected diabetes diagnosis.

revealing changes in cell type-specific gene expression programs, cell subpopulations, and transcriptional alterations in diabetes [85]. Similar single-cell analyses of pancreas tissue from different pancreas sources will significantly advance our understanding of heterogeneity in healthy and diseased metabolic tissues, but there is a need to standardize technical procedures linked to the isolation and collection of pancreas samples, and only comparison of similar cohorts can overcome limitations linked to sampling variability. Using pancreas samples derived from pancreatic surgery, coupled with *in vivo* metabolic and specific evaluation, as previously described, could represent a reasonable option.

Concluding Remarks

Our review of pancreatic surgery in the context of periampullary tumors reveals several important knowledge gaps. A main goal in clinical practice is to identify new biomarkers to distinguish and define diabetes concomitant with diagnosis of pancreatic carcinoma so as to improve patient postoperative outcome. Further, in-depth comparison of all the most frequent causes of 3c diabetes (i.e., surgery-induced diabetes, chronic pancreatitis, and pancreatic tumors) will be necessary to understand whether or not there is a common mechanism and how it can be correlated to the known and/or still unidentified mechanisms underlying type 2 diabetes. However, the use of samples and metabolic information from patients who undergo pancreatic surgery remains the model with the highest potential to improve knowledge and advance research in the field of islet biology and its correlated metabolic pathways (Box 2).

In conclusion, our model enables the collection of multiple snapshots of the natural history of patients through to the manifestation of diabetes or the preservation of normal glucose metabolism as a result of islet hyperplasia. The alignment of the different snapshots allows the best insights into islet plasticity, and has the advantage of studying *in vivo* endocrine and metabolic pathways and avoiding the problems of post-mortem pancreatic degeneration. The selection of samples on the basis of the above indications could lead to an improved understanding of the potential pancreatic disease- and/or tumor-induced triggers (see Outstanding Questions).

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Outstanding Questions

Do pancreatic diseases cause diabetes, and does diabetes cause pancreatic cancer?

What is the role of pre-existing islet remodeling in the pathogenesis of secondary diabetes?

Do pancreatic diseases alter islet morphology and function?

Should we put more effort into establishing clear and widely accepted criteria for the diagnosis of type 3c diabetes related to pancreatic disease compared with 'accelerated' type 2 diabetes? Alternatively, should the field focus instead on discovering biomarkers (if any) to distinguish between different types of glucose dysregulation before surgery?

Will the correlation between *ex vivo* islets and *in vivo* hormonal secretion cast light on the pathogenesis of type 2 diabetes?

What trigger in islet plasticity drives islets to cope adequately with insulin resistance or to fail, thus causing diabetes?

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