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Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer

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Abstract

Diabetes mellitus is a group of diseases defined by persistent hyperglycaemia. Type 2 diabetes, the most prevalent form, is characterised initially by impaired insulin sensitivity and subsequently by an inadequate compensatory insulin response. Diabetes can also develop as a direct consequence

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Contributors

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of other diseases, including diseases of the exocrine pancreas. Historically, diabetes due to diseases of the exocrine pancreas was described as pancreatogenic or pancreatogenous diabetes mellitus, but recent literature refers to it as type 3c diabetes. It is important to note that type 3c diabetes is not a single entity; it occurs because of a variety of exocrine pancreatic diseases with varying mechanisms of hyperglycaemia. The most commonly identified causes of type 3c diabetes are chronic pancreatitis, pancreatic ductal adenocarcinoma, haemochromatosis, cystic fibrosis, and previous pancreatic surgery. In this Review, we discuss the epidemiology, pathogenesis, and clinical relevance of type 3c diabetes secondary to chronic pancreatitis and pancreatic ductal adenocarcinoma, and highlight several important knowledge gaps.

Introduction

Diabetes mellitus is a group of diseases defined by persistent hyperglycaemia.¹ The most prevalent form is type 2 diabetes, which is characterised initially by impaired insulin sensitivity and subsequently by an inadequate compensatory insulin response. However, diabetes can also develop as a direct consequence of other diseases, including diseases of the exocrine pancreas.

Historically, diabetes due to diseases of the exocrine pancreas was described as pancreatogenic or pancreatogenous diabetes mellitus, but recent literature refers to it as type 3c diabetes. The origin of this term is attributed to a table published annually by the American Diabetes Association until 2014,² which listed four broad types of diabetes in an outline format with III.C indicating diabetes secondary to diseases of the exocrine pancreas, which authors have variably referenced as type IIIC diabetes mellitus and type 3c diabetes mellitus. We favour the term type 3c diabetes mellitus because the use of an Arabic numeral avoids confusion between the Roman numerals for two and three, and is consistent with nomenclature used for type 1 and type 2 diabetes. The lower case “c” is most commonly used in existing literature, so we have also adopted this. However, in contrast to type 1 and type 2 diabetes, it is important to recognise that the term type 3c diabetes incorporates causes of diabetes with different pathophysiologies, which are combined solely for the purposes of classification (panel).

Additional understanding of the different causes of type 3c diabetes is needed to allow us to more precisely define (and name) the different subtypes. We anticipate this nomenclature will undergo future refinement. The two major causative factors in the pathogenesis of diabetes are inadequate pancreatic β -cell function and insulin resistance. These two factors appear to contribute differentially to the hyperglycaemia observed in patients with type 3c diabetes. A comprehensive explanation of the physiology and methods of analysing insulin action and secretion is beyond the scope of this Review, but a synopsis is provided for context in the appendix.

The most commonly identified cause of type 3c diabetes is chronic pancreatitis. For example, in a large single-centre review, the distribution of causes for type 3c diabetes consisted of chronic pancreatitis (79%), pancreatic ductal adenocarcinoma (8%), haemochromatosis (7%), cystic fibrosis (4%), and previous pancreatic surgery (2%; figure).³ The following discussion will focus on type 3c diabetes secondary to chronic pancreatitis

and pancreatic ductal adenocarcinoma on the basis of their disease prevalence and clinical significance.

Estimated prevalence

The true worldwide prevalence of type 3c diabetes is unknown, but there are two possible approaches to generate an estimate. The first approach applies the reported prevalence of diabetes in pancreatic diseases from cohort studies to a broader population. Globally, the incidence of chronic pancreatitis is estimated at 33.7 cases per 100000 person-years and pancreatic ductal adenocarcinoma 8.1 cases per 100000 person-years.⁴ In the USA, the estimated number of prevalent cases of chronic pancreatitis is 150 000–175 000 and of pancreatic ductal adenocarcinoma is 50 000.^{5,6} Application of the prevalence of diabetes in chronic pancreatitis (up to about 80%) and pancreatic ductal adenocarcinoma (about 50%) to these estimates would yield at least 150000 cases of type 3c diabetes, or approximately 0.5–1% of all patients with diabetes (based on a US prevalence of 22 million in 2014). The second approach is to determine the prevalence of pancreatic diseases in a cohort of patients with diabetes, then apply this estimate to everyone in the population with diabetes. The largest study to assess prevalence among a cohort with diabetes classified 172 (9.2%) of 1868 as having type 3c diabetes.³ However, several factors are likely to have inflated this prevalence, including unresolved questions regarding whether or not the test abnormalities observed (eg, decreased faecal elastase-1 value) are a consequence of a disease of the exocrine pancreas or a secondary effect of diabetes (recently termed diabetic exocrine pancreatopathy⁷). A smaller study in 150 participants with diabetes reported a 5.4% prevalence of type 3c diabetes.⁸ Until additional studies are completed, it is reasonable to assume that the true prevalence of type 3c diabetes probably ranges from 1% to 9% of patients with diabetes, and 4–5% might be a reasonable working estimate.

Diagnostic criteria for type 3c diabetes

There are no universally accepted diagnostic criteria for type 3c diabetes. Conceptually, the diagnosis can be made in patients who meet the three following criteria: those who fulfil the diagnostic criteria for diabetes, those who have a disease of the exocrine pancreas, and those whose diabetes is reasonably certain to be secondary to their exocrine pancreatic disease.

In the only published criteria for type 3c diabetes, Ewald and Bretzel⁹ proposed the following major criteria (all must be present): exocrine pancreatic insufficiency (by monoclonal faecal elastase-1 testing or direct function tests), consistent pancreatic abnormalities on imaging (endoscopic ultrasound, MRI, or CT scan), and absence of related autoimmune markers of type 1 diabetes.⁹ Minor criteria included impaired β -cell function (as measured by homoeostatic model assessment for β -cell function, or C-peptide or glucose concentrations), absence of insulin resistance (as defined by homoeostatic model assessment for insulin resistance), impaired incretin secretion (glucagon-like peptide-1 [GLP-1] or pancreatic polypeptide, or both), and low serum concentrations of lipid soluble vitamins (A, D, E, and K). However, these criteria are limited by several important factors, including overlap of features with long-standing type 1 and 2 diabetes (appendix), little standardisation in methods used to determine inadequate β -cell function and insulin resistance, absence of

high-quality published data for glucose homeostasis in type 3c diabetes, the presence of coexistent insulin resistance in many patients, and the availability of adequate radiological and laboratory resources. Clinical characteristics of patients could help to further refine diagnostic criteria (appendix). In the absence of a definitive marker, the causality of diabetes due to exocrine disease is made either by the presence of advanced destruction or surgical removal of the pancreas, or recent onset of diabetes in the setting of pancreatic ductal adenocarcinoma.

Diabetes secondary to chronic pancreatitis

Type 3c diabetes is a frequent comorbidity of chronic pancreatitis, with prevalence estimates ranging from 25% to 80%.^{10–14} Increased disease duration is an important risk factor for diabetes secondary to chronic pancreatitis. In hereditary pancreatitis, the median age of onset of diabetes is between 38 and 53 years, but the age of onset of diabetes is less well characterised in the acquired forms of chronic pancreatitis.^{11,12}

During the past two decades, there have been tremendous advancements in understanding of the genetic determinants of chronic pancreatitis, which predominantly modify the risk for development and progression of disease.¹⁵ However, no systematic studies to date have examined the potential genetic differences between type 3c diabetes secondary to chronic pancreatitis (or pancreatic cancer) and type 2 diabetes (or other subtypes of diabetes).

Complications

Data for acute metabolic complications, such as hypoglycaemia and diabetic ketoacidosis, in pancreatic disorders are scarce. In one series of 36 patients with diabetes associated with chronic pancreatitis, 78% of those treated with insulin reported hypoglycaemia and 17% had severe hypoglycaemia.¹⁶ Data for traditional target organ complications from type 3c diabetes are similarly scarce. In the only prospective study to date, 54 patients with type 3c diabetes due to chronic pancreatitis or total pancreatectomy were studied.¹⁷ The risk of diabetic retinopathy was 31% and correlated with the duration of diabetes. In separate studies, diabetic retinopathy (37%), diabetic nephropathy (29%), and peripheral arterial disease (26%) developed in patients from the respective cohorts.^{18,19} However, many of these studies were published decades ago with variable study designs, so extrapolations of available data are not reliable. Prospectively, smoking, hypertension, hyperlipidaemia, and obesity are expected to influence target organ complications and should be studied concurrently with type 3c diabetes.

Increased risk of pancreatic cancer

Because both diabetes mellitus and chronic pancreatitis are risk factors for pancreatic ductal adenocarcinoma, the combination might particularly increase concern for progression to pancreatic ductal adenocarcinoma.²⁰ In a population-based cohort study in Taiwan, the risk of pancreatic ductal adenocarcinoma was substantially elevated in participants with concurrent diabetes and chronic pancreatitis (hazard ratio 33.5).²¹ Separate database studies also showed an increased, but more modest, risk ratio (4.7–12.1) of pancreatic ductal

adenocarcinoma in those with otherwise unclassified diabetes and a history of chronic pancreatitis.^{22,23} Additional validation in other cohorts is needed.

Mechanisms of hyperglycaemia

Insulin deficiency—A key mechanism underlying the high risk of diabetes in chronic pancreatitis is deficient insulin production. Cross-sectional studies of patients with chronic pancreatitis suggest progressive insulin deficiency, with mild insulin deficiency present even before the development of diabetes, but more severe deficiency in chronic pancreatitis with type 3c diabetes.^{24,25} In another cross-sectional study of patients without diabetes but with chronic pancreatitis, some of whom had impaired fasting glucose, the disposition index (a measure of insulin secretion adjusted for insulin sensitivity from the frequently sampled intravenous glucose tolerance test) was lower in the chronic pancreatitis group than in healthy controls matched for age, sex, and body-mass index, with the most pronounced deficits in those with chronic calcific pancreatitis.²⁶ Endocrine function tends to decline in parallel with exocrine function, although frank diabetes is likely to occur later in the course of the disease.²⁷

Two potential mechanisms might underlie this clinical observation of relative insulin deficiency. First, even early in the course of chronic pancreatitis, the inflammatory environment and increased concentration of cytokines within the pancreatic parenchyma have been postulated to mediate β -cell dysfunction before frank β -cell loss.²⁸ Second, as chronic pancreatitis progresses, the extensive fibrosis of the exocrine pancreas slowly destroys the pancreatic islet tissue. Decreased insulin secretion in diabetes secondary to chronic pancreatitis has been shown to correlate with decreased pancreatic and β -cell mass, which is the mechanism of type 3c diabetes after partial or total pancreatectomy.²⁹

Potential immunopathogenesis—Inhibition of glucose-stimulated insulin release by proinflammatory cytokines, including interleukin 1 β , tumour necrosis factor (TNF) α , and interferon γ , has been demonstrated.³⁰ Islets expressing high concentrations of interleukin 1R and interleukin 1 β induce β -cell apoptosis.³¹ Clinical studies of antagonists to interleukin 1R, interleukin 1 β , and TNF α have shown some efficacy in type 2 diabetes.³² Increased expression of interferon γ results in impaired translocation of the islet cell transcription factor PDX-1 in patients with chronic pancreatitis.³³ This loss of PDX-1 localisation to the nucleus can be reversed by specific inhibition of interferon γ . Additionally, adrenomedullin and vanin-1, which are also expressed in response to inflammation, probably play an important part in altered islet cell function in type 3c diabetes caused by both chronic pancreatitis and pancreatic ductal adenocarcinoma.³⁴ Studies are needed to further examine these inflammatory mediators, as well as the role of interleukin 10, interleukin 12, and other cytokines in diabetes secondary to chronic pancreatitis (appendix), to better contrast the different immunopathogenesis compared with type 2 diabetes.

Hepatic insulin resistance—Hepatic insulin resistance has been demonstrated in patients with type 3c diabetes secondary to pancreatic resection, chronic pancreatitis, pancreatic ductal adenocarcinoma, and cystic fibrosis.^{35–38} The cause of persistent hepatic

glucose production and isolated hepatic insulin resistance in type 3c diabetes appears to be multifactorial, with a deficient pancreatic polypeptide response playing a key part (appendix). Pancreatic polypeptide regulates the expression and availability of hepatic insulin receptors, and the diminished insulin receptor availability in chronic pancreatitis can be reversed by pancreatic polypeptide administration.^{39–41} Data from clamp studies in patients with pancreatic polypeptide deficiency and chronic pancreatitis showed that pancreatic polypeptide administration reversed the hepatic insulin resistance.³⁶ In a subsequent randomised, blinded, placebo-controlled study, a 72 h subcutaneous infusion of pancreatic polypeptide improved overall insulin sensitivity in pancreatic polypeptide-deficient patients with type 1 and type 3c diabetes.⁴² Pancreatic polypeptide deficiency is a common finding in all forms of type 3c diabetes studied thus far, and these studies show that pancreatic polypeptide is a glucoregulatory hormone that regulates hepatic insulin sensitivity.

In addition to altered insulin receptor availability, altered hepatic insulin function in chronic pancreatitis has also been linked to the inflammation-based activation of hepatocyte I- κ B kinase- β and NF- κ B.⁴³ Blockade of NF- κ B activation results in improved hepatic insulin sensitivity.⁴⁴ This effect can be achieved by activation of peroxisome proliferator-activated receptor- γ , which is the mechanism of action of the thiazolidinedione class of antidiabetic drugs. Rosiglitazone has been shown to reverse hepatic insulin resistance in rats with chronic pancreatitis, but has not been rigorously studied in human beings.⁴⁵

Peripheral insulin resistance—Accurate methods for measurement of insulin sensitivity and insulin secretion (including the euglycaemic–hyperinsulinaemic clamp and frequently sampled intravenous glucose tolerance test) have demonstrated the presence of insulin resistance in chronic pancreatitis. Insulin resistance is commonly observed and appears to be independent of other components of the metabolic syndrome.⁴⁶ In clamp studies of patients with both chronic pancreatitis and diabetes, the degree of total-body insulin sensitivity (which primarily reflects peripheral insulin-mediated glucose uptake) was less than that observed in healthy controls or in patients with type 1 diabetes.^{47,48} Another clamp study using tracers (which can assess endogenous [hepatic] glucose production, and are normally suppressed by insulin) found elevated basal endogenous glucose production that was suppressible during hyperinsulinaemic infusion in patients with type 3c diabetes compared with controls.⁴⁸ By contrast, one group's clamp studies showed increased insulin sensitivity in patients with type 3c diabetes compared with type 1 diabetes.^{49,50} These studies suggest that insulin resistance is probably a contributing factor to diabetes secondary to chronic pancreatitis; however, further studies are needed to confirm this notion, and establish whether the observed insulin resistance is a cause or consequence of hyperglycaemia.

Reduced incretin effect—The incretin effect refers to the greater insulin response observed with oral glucose loading compared with an equivalent intravenous glucose load. This effect is mainly mediated by rapid meal-induced secretion of hormone signals from the gastrointestinal tract that promote insulin secretion (enteroinsular axis). The primary incretin hormones are glucose-dependent insulintropic polypeptide (GIP), which is secreted by K

cells in the small intestine, and GLP-1, which is mainly secreted by L cells in the ileum and large intestine. Both of these hormones are rapidly inactivated by dipeptidyl peptidase 4 (DPP-4), and augment insulin secretion in a glucose-dependent manner. In type 2 diabetes, deficient secretion of GLP-1 and resistance to GIP has been suggested.⁵¹ In type 3c diabetes, the sensitivity to GLP-1 seems to be intact, while the late-phase insulin secretion response to GIP is reduced similarly to that in type 2 diabetes.^{52–54}

Because many patients with chronic pancreatitis often develop exocrine pancreatic insufficiency, a leading hypothesis is that impaired nutrient absorption might result in a reduced incretin response to meals, with consequently reduced postprandial insulin secretion. However, results of studies have been mixed in this regard and some investigators have concluded that the reduced incretin effect is a consequence, not a cause, of the diabetic state.^{55–57} Additional studies have had discrepant results, which might be a consequence of small sample size (<ten participants in each group) and inaccurate incretin assays. These conflicting reports suggest the need for a comprehensive examination of basal and stimulated incretin responses.

Interactions between exocrine pancreatic insufficiency and glucose homeostasis

Given that nutrient ingestion stimulates incretin secretion, investigators have sought to establish whether pancreatic enzyme replacement therapy (PERT) for patients with exocrine pancreatic insufficiency would stimulate incretin secretion, thereby improving glycaemic control. The premise is that digestion and absorption of nutrients, not simply their luminal presence, might be important for incretin production. The table shows the available data characterising incretin, glycaemic, and pancreatic islet hormonal responses to PERT in patients with chronic pancreatitis and cystic fibrosis.^{55,57–59} These small, but well done, studies assessed hormonal responses with and without PERT with a meal challenge. Despite the heterogeneity of these studies, they uniformly showed that PERT resulted in increased postprandial responses in GIP and GLP-1; however, the predicted concomitant increase in insulin response was observed only in chronic pancreatitis. It has also been suggested that improved glycaemic control in type 2 diabetes can improve the incretin response, so additional efforts are needed to understand these complex relationships. The available data are compelling, but further studies are needed to investigate the use of PERT in patients with chronic pancreatitis to assess the potential to improve glycaemic control.

Management of hyperglycaemia

There are no head-to-head comparison studies to determine the relative safety and efficacy of available antidiabetic therapies in chronic pancreatitis. Thus, treatment is extrapolated from the pathophysiology of diabetes secondary to chronic pancreatitis and the known risk of pancreatic ductal adenocarcinoma in the setting of chronic pancreatitis and diabetes. Metformin or insulin is used as first-line therapy, and their use might be tailored to the specific presentation of the patient. Available data from cohort studies suggest that at least half of those with diabetes secondary to chronic pancreatitis are treated with insulin therapy.^{10,11} Insulin therapy addresses the insulin deficiency present in the disease, which is recommended by consensus guidelines in advanced diabetes secondary to chronic pancreatitis.⁶⁰ However, there is a risk of hypoglycaemia with insulin therapy, particularly in

patients with chronic pancreatitis who might have enhanced peripheral insulin sensitivity.⁶¹ By contrast, early in the course of diabetes secondary to chronic pancreatitis, particularly if hyperglycaemia is mild ($\text{HbA}_{1c} < 8\%$ or $< 64 \text{ mmol/mol}$), metformin alone might be considered as a first-line agent. Metformin has a theoretical advantage compared with insulin, in that it might be protective against pancreatic ductal adenocarcinoma; however, findings from previous studies might not be extrapolated to the setting of chronic pancreatitis, which has a different physiology to that of type 2 diabetes, particularly with regards to the presence of insulin deficiency in chronic pancreatitis compared with hyperinsulinism in type 2 diabetes.

The role of other antidiabetic agents is unclear. The incretin-based therapies—injectable GLP-1 analogues and oral DPP-4 inhibitors—are typically avoided in chronic pancreatitis because of their potential role in increasing risk for acute pancreatitis and pancreatic ductal adenocarcinoma.⁶² The thiazolidinediones increase both hepatic and peripheral insulin sensitivity but carry an increased risk of bone fracture, so their use might not be well suited for patients who are already at increased risk for this complication.

Diabetes secondary to pancreatic cancer

The association between pancreatic ductal adenocarcinoma and diabetes has been recognised for more than 150 years, and has been examined in more than 50 case-control and cohort studies. Meta-analyses of these studies have consistently shown a 1.5–2 times increased risk of pancreatic ductal adenocarcinoma in patients with long-standing (> 5 years) diabetes, and a greater risk in individuals with diabetes duration of less than 5 years. Type 2 diabetes is associated with insulin resistance, variable insulin concentrations, an inability of the liver to suppress inappropriate hepatic glucose release, and an inability of the β cells to overcome insulin resistance. In addition to β -cell dysfunction mediated by inflammation, β -cell loss can occur as a consequence of oxidative stress and aberrant activation of the unfolded protein response pathway, which can induce both apoptosis and cell senescence leading to a decreased β -cell mass.^{63,64} Additionally, type 2 diabetes is often associated with obesity, which independently increases the risk for developing pancreatic ductal adenocarcinoma.⁶⁵ Both conditions can lead to increased insulin in the pancreatic microenvironment, which promotes tumour development (appendix). Collectively, these changes are believed to partly explain the modest increased risk for pancreatic ductal adenocarcinoma in those with long-standing type 2 diabetes.

In a meta-analysis, Ben and colleagues⁶⁶ reported a relative risk of 5.4 (95% CI 3.5–8.3) associated with diabetes of less than 1 year duration, with modest risk of about 1.5 times after 5 years of diabetes. Although the vast majority ($> 95\%$) of patients older than 50 years with new-onset diabetes have type 2 diabetes, a small proportion has a variety of other causes of diabetes (eg, late-onset type 1 diabetes, Cushing's syndrome, or chronic pancreatitis). A population-based study from Rochester, MN, USA, found that approximately 1% of participants with new-onset diabetes at age 50 years or older have diabetes secondary to pancreatic cancer.⁶⁷ In other studies, subsets of participants with recently diagnosed diabetes have been found to have an even higher prevalence of pancreatic ductal adenocarcinoma (5.2–13.6%).^{68–70} Thus, although long-standing diabetes modestly

increases the risk of pancreatic ductal adenocarcinoma, new-onset diabetes appears to be a marker of underlying pancreatic ductal adenocarcinoma in an important subset.

Hypotheses for increased prevalence of diabetes

Shared risk factors—Because canonical risk factors for type 2 diabetes—eg, old age, obesity, and family history of diabetes—are also risk factors for diabetes secondary to pancreatic cancer, there is a possibility that increased prevalence of diabetes in pancreatic ductal adenocarcinoma is an artifact of screening for diabetes in an elderly population.⁷¹ However, a study comparing the prevalence of diabetes in common cancers (breast, lung, prostate, and colon) showed no increased prevalence of diabetes compared with age-matched controls, although the high prevalence of diabetes in pancreatic ductal adenocarcinoma, especially recent-onset diabetes, was confirmed.⁷²

Glandular destruction—If the diabetes observed in pancreatic ductal adenocarcinoma were a consequence of glandular destruction, hypoinsulinaemia would be expected; however, diabetes secondary to pancreatic cancer is associated with hyperinsulinaemia secondary to insulin resistance. In fact, the median duration of diabetes in pancreatic ductal adenocarcinoma is about 13 months, at a time when imaging studies show no visible tumour.^{73,74} Moreover, 60% of small tumours (<20 mm in size) are associated with glucose intolerance, and more than half of patients with resectable tumours have diabetes.^{71,72,75} Thus, there is insufficient evidence to support the hypothesis that diabetes secondary to pancreatic cancer is due to local effects of tumour infiltration, ductal obstruction, and consequently glandular destruction.⁷⁶

Pancreatic ductal adenocarcinoma causes diabetes—The markedly increased risk of pancreatic ductal adenocarcinoma in new-onset diabetes appears to be due to reverse causality—ie, pancreatic ductal adenocarcinoma causes hyperglycaemia. This notion is supported by a large body of clinical, epidemiological, and experimental evidence. First, there is an exceedingly high prevalence of diabetes in the setting of pancreatic ductal adenocarcinoma, irrespective of the method of diagnosis. Approximately 80% of patients with pancreatic ductal adenocarcinoma have abnormal fasting glucose or glucose intolerance regardless of tumour size or stage.^{37,71,77} When formally tested with oral glucose tolerance tests, nearly two-thirds of patients with pancreatic ductal adenocarcinoma have diabetes.^{37,77,78} When screened for diabetes with fasting glucose, the prevalence is about 45%.⁷¹ Second, the onset of diabetes is often temporally related to the diagnosis of pancreatic ductal adenocarcinoma.⁷⁹ Most patients (75–88%) reported that diabetes was new onset—ie, diagnosed less than 24–36 months before diagnosis of pancreatic ductal adenocarcinoma.^{73,80,81} Third, effective treatment of pancreatic ductal adenocarcinoma often leads to improvement in hyperglycaemia for those with new-onset diabetes secondary to pancreatic cancer. Resection of the tumour improves or resolves diabetes in many patients with new-onset diabetes, although there is no improvement in those with long-standing diabetes.⁷¹ Similarly, the metabolic defects are improved in those who have a treatment response to chemotherapy.⁸² Lastly, pancreatic tumours might indirectly induce hyperglycaemia. Addition of conditioned media from pancreatic ductal adenocarcinoma cell

lines impairs glucose metabolism in vitro in peripheral tissues and inhibits insulin release from β -cell lines.^{83–86}

Mechanisms of hyperglycaemia

Insulin resistance—Type 3c diabetes due to pancreatic ductal adenocarcinoma appears to differ fundamentally from other causes of type 3c diabetes in that it is not due to fibro-inflammatory destruction or pancreatectomy. Rather, the previous line of reasoning indicates diabetes secondary to pancreatic cancer is probably a paraneoplastic effect due to mediators released by the cancer.⁷⁶ However, the mechanisms of diabetes remain uncertain, with evidence suggesting that both insulin resistance and β -cell dysfunction improve with cancer resection in pancreatic ductal adenocarcinoma.

Whole body physiology studies have consistently shown that diabetes in pancreatic ductal adenocarcinoma is associated with substantial insulin resistance.⁷⁸ In a series of studies, primarily performed by Permert and colleagues,^{77,78,87–89} there is decreased glucose metabolic capacity (ie, insulin resistance) in participants with pancreatic ductal adenocarcinoma, which is more pronounced in participants with diabetes, but also present in those with normoglycaemia and pancreatic ductal adenocarcinoma. Therefore, investigators have sought to identify putative mediators of insulin resistance in pancreatic ductal adenocarcinoma. In an early study, investigators showed that concentrations of plasma islet amyloid polypeptide were elevated in participants with pancreatic ductal adenocarcinoma who have diabetes, and they postulated that it might contribute to the pathogenesis; however, subsequent studies failed to validate this observation, so the hypothesis has not been further investigated.^{80,90} Thus, the mechanism of insulin resistance in pancreatic ductal adenocarcinoma needs further study.

β -cell dysfunction—An impaired β -cell response to oral glucose load, hyperglycaemic clamp, and glucagon stimulation has been shown in diabetes secondary to pancreatic cancer.^{37,88,91–93} In studies using the homeostatic model assessment, β -cell function was markedly diminished in pancreatic ductal adenocarcinoma with impaired fasting glucose, whereas insulin resistance was only modestly increased.⁸⁹ A β -cell toxic secretory product of pancreatic ductal adenocarcinoma has long been postulated based on the fact that supernatant from cell lines of pancreatic ductal adenocarcinoma inhibited insulin secretion.⁹⁴ Microarray analysis of diabetogenic cell lines of pancreatic ductal adenocarcinoma led to identification of adrenomedullin as a candidate mediator of this effect.^{83,95} Adrenomedullin was shown to mediate pancreatic ductal adenocarcinoma-induced inhibition of insulin secretion in β cells in various in-vitro and in-vivo tumour models of pancreatic ductal adenocarcinoma.⁸³ Plasma concentrations of adrenomedullin were higher in participants with diabetes secondary to pancreatic cancer compared with those without diabetes and healthy controls.⁸³ Adrenomedullin has previously been shown to be overexpressed in pancreatic ductal adenocarcinoma and enhances tumour aggressiveness.^{96–98} Thus, adrenomedullin, secreted by the cancerous pancreas in its hostile microenvironment, not only promoted invasive behaviour but also caused hyperglycaemia. Subsequently, adrenomedullin was identified in exosomes secreted by cancer cell lines, and

the effect of these supernatants on insulin secretion was shown to be mediated by adrenomedullin contained in exosomes.^{99,100}

Influence of adipokines—Adipokines have been associated with the development of diabetes, obesity, and pancreatic ductal adenocarcinoma.^{101,102} Some of these adipokines have been proposed as potential biomarkers for early detection of pancreatic ductal adenocarcinoma, and are also believed to have a role in tumour development.^{102,103} One of these candidate markers, lipocalin 2 (LCN2; also known as neutrophil gelatinase associated lipocalin [NGAL]), has also been described in obesity associated with breast cancer.^{104–106} LCN2 is elevated in the serum and visceral adipose tissue of obese individuals, and regulates adipose inflammation affecting glucose metabolism and insulin sensitivity.^{104,107} Other adipokines of interest in obesity-associated pancreatic ductal adenocarcinoma include leptin and adiponectin.^{108,109}

Potential immunopathogenesis—Increased calprotectin (S100A8/A9) is detected in inflammation and various types of cancers.¹¹⁰ The N-terminus of the S100-A8 peptide has been proposed as a potential diabetogenic factor on the basis of proteomic findings in samples of pancreatic ductal adenocarcinoma, as well as observation of glucose utilisation of myoblasts exposed to the peptide.¹¹¹ Another proteomic study found upregulation of S100-A9 in pancreatic ductal adenocarcinoma tissues with diabetes compared with those without diabetes.¹¹² S100A8/A9 is highly abundant in neutrophils and activated monocytes or macrophages, and these findings might reflect the myeloid cell infiltration observed even at early stages of pancreatic ductal adenocarcinoma development.^{113,114} A study using peripheral blood mononuclear cell gene profiling for pancreatic ductal adenocarcinoma proposed vanin-1 and matrix metalloproteinase-9 (MMP9) as biomarkers to discriminate diabetes secondary to pancreatic cancer from type 2 diabetes.³⁴ A more recent study of blood and tissue mRNA also associated increased expression of MMP9, but not S100-A8, with diabetes secondary to pancreatic cancer.¹¹⁵ Macrophages upregulate MMP9 and S100-A8 in response to TNF α and interleukin 1 β —cytokines enriched in the tumour microenvironment.^{116–118} Additional insights suggest that this inflammatory environment might partly explain the β -cell dysfunction observed in pancreatic ductal adenocarcinoma, representing an important area of future research (appendix).

Clinical relevance

The new occurrence of diabetes in the context of pancreatic ductal adenocarcinoma has important clinical implications.¹¹⁹ New-onset diabetes might potentially be used for early detection of pancreatic ductal adenocarcinoma since it often comes before clinical diagnosis of pancreatic ductal adenocarcinoma by up to 24–36 months. In one study, 0.85% of participants with new-onset diabetes older than 50 years had pancreatic ductal adenocarcinoma.⁶⁷ However, in view of this low prevalence of pancreatic ductal adenocarcinoma in the cohort of people with new-onset diabetes, additional features are needed to identify the high-risk population. Although typical demographic features and family history of diabetes do not discriminate between type 2 diabetes and diabetes secondary to pancreatic cancer, weight loss at the time of diabetes onset is more common in pancreatic ductal adenocarcinoma than in type 2 diabetes (59% vs 30%; $p=0.02$).¹²⁰ A

recent study also showed a blunted serum pancreatic polypeptide response to mixed meal stimulation in those with new-onset diabetes secondary to pancreatic cancer compared with type 2 diabetes.¹²¹ However, the abnormal response was not observed in those with a tumour located on the body or tail of the pancreas, so this test might need to be coupled with other screening measures if the results are validated.

Additionally, diabetes is associated with negative clinical outcomes in those with pancreatic ductal adenocarcinoma. The presence of diabetes has also been identified as a predictor of worse survival in all stages of disease.^{122,123} Patients with diabetes also have increased risk of complications after surgery for pancreatic ductal adenocarcinoma, including pancreatic leaks, surgical site infections, intra-abdominal abscesses, and delayed gastric emptying.¹²⁴ However, to demonstrate causality between diabetes and these outcomes in pancreatic ductal adenocarcinoma is challenging because of the organ's role in glucose homeostasis, potential influence (positive or negative) of antidiabetic medications, variable glycaemic responses (including paradoxical improvement) after cancer-related treatments, and influence of diabetes duration (which was often not accounted for in previous studies).

Management of hyperglycaemia

There are no direct studies to inform decisions regarding the management of hyperglycaemia in diabetes secondary to pancreatic cancer. By contrast with chronic pancreatitis and other forms of diabetes, prevention of the long-term sequelae of diabetes is less relevant in this group of patients because of the shortened life expectancy. Rather, the primary treatment goal is to prevent short-term metabolic complications, which can lead to morbidity and delay cancer-related treatments. Metformin is an attractive drug in this patient group because of its reported antineoplastic properties, and studies suggesting its use might confer protection from development of pancreatic ductal adenocarcinoma. In patients with type 2 diabetes, case-control studies have suggested up to a 60% reduction in the risk of pancreatic ductal adenocarcinoma with metformin treatment, although data from recent meta-analyses have shown mixed results.^{125–127} In two phase 2 trials in metastatic pancreatic ductal adenocarcinoma, there was no difference in progression-free or overall survival in those who received metformin in addition to a standard chemotherapeutic regimen.^{128,129} Other data, albeit controversial, suggest that insulin and incretin-based therapies (GLP-1 analogues and oral DPP-4 inhibitors) might increase risk for developing pancreatic ductal adenocarcinoma.¹³⁰ When hypoglycaemic agents are used, it is important to closely monitor glucose concentrations because the hyperglycaemia can improve, and often resolve, in those successfully treated with surgery or chemotherapy.^{71,82} Thus, metformin might be preferred as first-line therapy for mild hyperglycaemia, but there is a paucity of data to inform additional therapy.

Knowledge gaps

Our Review of type 3c diabetes reveals several important knowledge gaps. At a foundational level, a better understanding of the pathogenesis is needed to more accurately define and distinguish type 3c diabetes from other diabetes subtypes. Clinically, the associated pancreatic disorders are heterogeneous and preliminary data support the concept that the

mechanisms of hyperglycaemia differ in the various forms of type 3c diabetes. Further characterisation of the underlying mechanisms of disease, including genetic predispositions and physiological differences in β -cell function and insulin sensitivity, will help to discriminate the different forms of type 3c diabetes from the much more prevalent type 2 diabetes. These insights are needed to develop validated diagnostic criteria and accurate disease prevalence estimates, and will permit further investigations into the potential use of new-onset diabetes for early detection of pancreatic ductal adenocarcinoma and therapeutic interventions for type 3c diabetes.

Future studies

The Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) was formed in 2015 to undertake a comprehensive clinical, epidemiological, and biological characterisation of patients to understand the complex relationships between chronic pancreatitis (including recurrent acute pancreatitis), diabetes, and pancreatic ductal adenocarcinoma. The key driving forces behind this effort include the increased risk for developing pancreatic ductal adenocarcinoma in those with chronic pancreatitis, particularly those with diabetes, and the increasing mortality rate of pancreatic ductal adenocarcinoma, which is expected to become the second leading cause of cancer death in the USA by 2030.¹³¹ The CPDPC will enrol patients in longitudinal cohorts designed to identify biomarkers of these pancreatic diseases and more precisely define their relationships. These studies will address many of these gaps in knowledge, leading to earlier detection, prevention, and better treatment options for these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. American Diabetes Association. 2. Classification and diagnosis of diabetes. Diabetes Care. 2016; 39(suppl 1):S13–22. [PubMed: 26696675]
2. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 2003; 26(suppl 1):S5–20. [PubMed: 12502614]
3. Ewald N, Kaufmann C, Raspe A, Kloer HU, Bretzel RG, Hardt PD. Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c). Diabetes Metab Res Rev. 2012; 28:338–42. [PubMed: 22121010]
4. Xiao, AY., Tan, MLY., Wu, LM., et al. Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. Lancet Gastroenterol Hepatol. 2016. published online June 28. [http://dx.doi.org/10.1016/S2468-1253\(16\)30004-8](http://dx.doi.org/10.1016/S2468-1253(16)30004-8)

5. Yadav D, Timmons L, Benson JT, Dierkhising RA, Chari ST. Incidence, prevalence, and survival of chronic pancreatitis: a population-based study. *Am J Gastroenterol*. 2011; 106:2192–99. [PubMed: 21946280]
6. National Cancer Institute. SEER Cancer Statistics Factsheets: Pancreas Cancer. <http://seer.cancer.gov/statfacts/html/pancreas.html> (accessed April 21, 2016).
7. Mohapatra S, Majumder S, Smyrk TC, et al. Diabetes mellitus is associated with an exocrine pancreatopathy: conclusions from a review of literature. *Pancreas*. 2016; 45:1104–10. [PubMed: 26918874]
8. Vujasinovic M, Zaletel J, Tepes B, et al. Low prevalence of exocrine pancreatic insufficiency in patients with diabetes mellitus. *Pancreatology*. 2013; 13:343–46. [PubMed: 23890131]
9. Ewald N, Bretzel RG. Diabetes mellitus secondary to pancreatic diseases (type 3c)—are we neglecting an important disease? *Eur J Intern Med*. 2013; 24:203–06. [PubMed: 23375619]
10. Malka D, Hammel P, Sauvanet A, et al. Risk factors for diabetes mellitus in chronic pancreatitis. *Gastroenterology*. 2000; 119:1324–32. [PubMed: 11054391]
11. Rebours V, Boutron-Ruault MC, Schnee M, et al. The natural history of hereditary pancreatitis: a national series. *Gut*. 2009; 58:97–103. [PubMed: 18755888]
12. Howes N, Lerch MM, Greenhalf W, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. *Clin Gastroenterol Hepatol*. 2004; 2:252–61. [PubMed: 15017610]
13. Wang W, Guo Y, Liao Z, et al. Occurrence of and risk factors for diabetes mellitus in Chinese patients with chronic pancreatitis. *Pancreas*. 2011; 40:206–12. [PubMed: 21404458]
14. Larsen S, Hilsted J, Tronier B, Worning H. Metabolic control and β cell function in patients with insulin-dependent diabetes mellitus secondary to chronic pancreatitis. *Metabolism*. 1987; 36:964–67. [PubMed: 3309547]
15. Whitcomb DC. Genetic risk factors for pancreatic disorders. *Gastroenterology*. 2013; 144:1292–302. [PubMed: 23622139]
16. Linde J, Nilsson LH, Barany FR. Diabetes and hypoglycemia in chronic pancreatitis. *Scand J Gastroenterol*. 1977; 12:369–73. [PubMed: 867001]
17. Tiengo A, Segato T, Briani G, et al. The presence of retinopathy in patients with secondary diabetes following pancreatectomy or chronic pancreatitis. *Diabetes Care*. 1983; 6:570–74. [PubMed: 6653314]
18. Briani G, Riva F, Midena E, et al. Prevalence of microangiopathic complications in hyperglycemia secondary to pancreatic disease. *J Diabet Complications*. 1988; 2:50–52. [PubMed: 2968358]
19. Ziegler O, Candiloros H, Guerri B, Got I, Crea T, Drouin P. Lower-extremity arterial disease in diabetes mellitus due to chronic pancreatitis. *Diabetes Metab*. 1994; 20:540–45.
20. Cui Y, Andersen DK. Diabetes and pancreatic cancer. *Endocr Relat Cancer*. 2012; 19:F9–26. [PubMed: 22843556]
21. Liao KF, Lai SW, Li CI, Chen WC. Diabetes mellitus correlates with increased risk of pancreatic cancer: a population-based cohort study in Taiwan. *J Gastroenterol Hepatol*. 2012; 27:709–13. [PubMed: 21929650]
22. Munigala S, Singh A, Gelrud A, Agarwal B. Predictors for pancreatic cancer diagnosis following new-onset diabetes mellitus. *Clin Transl Gastroenterol*. 2015; 6:e118. [PubMed: 26492440]
23. Brodovicz KG, Kou TD, Alexander CM, et al. Impact of diabetes duration and chronic pancreatitis on the association between type 2 diabetes and pancreatic cancer risk. *Diabetes Obes Metab*. 2012; 14:1123–28. [PubMed: 22831166]
24. Domschke S, Stock KP, Pichl J, Schneider MU, Domschke W. β -Cell reserve capacity in chronic pancreatitis. *Hepatogastroenterology*. 1985; 32:27–30. [PubMed: 3886512]
25. Sherry NA, Tsai EB, Herold KC. Natural history of β -cell function in type 1 diabetes. *Diabetes*. 2005; 54(suppl 2):S32–39. [PubMed: 16306337]
26. Lundberg R, Beilman GJ, Dunn TB, et al. Early alterations in glycemic control and pancreatic endocrine function in nondiabetic patients with chronic pancreatitis. *Pancreas*. 2016; 45:565–71. [PubMed: 26918872]

27. Nyboe Andersen B, Krarup T, Thorsgaard Pedersen NT, Faber OK, Hagen C, Worning H. β cell function in patients with chronic pancreatitis and its relation to exocrine pancreatic function. *Diabetologia*. 1982; 23:86–89. [PubMed: 6182047]
28. Sasikala M, Talukdar R, Pavan kumar P, et al. β -cell dysfunction in chronic pancreatitis. *Dig Dis Sci*. 2012; 57:1764–72. [PubMed: 22383081]
29. Schrader H, Menge BA, Schneider S, et al. Reduced pancreatic volume and β -cell area in patients with chronic pancreatitis. *Gastroenterology*. 2009; 136:513–22. [PubMed: 19041312]
30. Andersson AK, Flodstrom M, Sandler S. Cytokine-induced inhibition of insulin release from mouse pancreatic β -cells deficient in inducible nitric oxide synthase. *Biochem Biophys Res Commun*. 2001; 281:396–403. [PubMed: 11181061]
31. Boni-Schnetzler M, Boller S, Debray S, et al. Free fatty acids induce a proinflammatory response in islets via the abundantly expressed interleukin-1 receptor I. *Endocrinology*. 2009; 150:5218–29. [PubMed: 19819943]
32. Donath MY. Targeting inflammation in the treatment of type 2 diabetes: time to start. *Nat Rev Drug Discov*. 2014; 13:465–76. [PubMed: 24854413]
33. Pondugala PK, Sasikala M, Guduru VR, Rebala P, Nageshwar Reddy D. Interferon- γ decreases nuclear localization of Pdx-1 and triggers β -cell dysfunction in chronic pancreatitis. *J Interferon Cytokine Res*. 2015; 35:523–29. [PubMed: 25839229]
34. Huang H, Dong X, Kang MX, et al. Novel blood biomarkers of pancreatic cancer-associated diabetes mellitus identified by peripheral blood-based gene expression profiles. *Am J Gastroenterol*. 2010; 105:1661–69. [PubMed: 20571492]
35. Seymour NE, Brunicaudi FC, Chaiken RL, et al. Reversal of abnormal glucose production after pancreatic resection by pancreatic polypeptide administration in man. *Surgery*. 1988; 104:119–29. [PubMed: 3041640]
36. Brunicaudi FC, Chaiken RL, Ryan AS, et al. Pancreatic polypeptide administration improves abnormal glucose metabolism in patients with chronic pancreatitis. *J Clin Endocrinol Metab*. 1996; 81:3566–72. [PubMed: 8855802]
37. Cersosimo E, Pisters PW, Pesola G, McDermott K, Bajorunas D, Brennan MF. Insulin secretion and action in patients with pancreatic cancer. *Cancer*. 1991; 67:486–93. [PubMed: 1985741]
38. Kien CL, Horswill CA, Zipf WB, McCoy KS, O'Dorisio T. Elevated hepatic glucose production in children with cystic fibrosis. *Pediatr Res*. 1995; 37:600–05. [PubMed: 7603777]
39. Seymour NE, Turk JB, Laster MK, et al. In vitro hepatic insulin resistance in chronic pancreatitis in the rat. *J Surg Res*. 1989; 46:450–56. [PubMed: 2654478]
40. Seymour NE, Volpert AR, Lee EL, Andersen DK, Hernandez C. Alterations in hepatocyte insulin binding in chronic pancreatitis: effects of pancreatic polypeptide. *Am J Surg*. 1995; 169:105–09. [PubMed: 7817978]
41. Goldstein JA, Kirwin JD, Seymour NE, Trachtenberg JE, Rademaker EA, Andersen DK. Reversal of in vitro hepatic insulin resistance in chronic pancreatitis by pancreatic polypeptide in the rat. *Surgery*. 1989; 106:1128–32. [PubMed: 2588116]
42. Rabiee A, Galiatsatos P, Salas-Carrillo R, Thompson MJ, Andersen DK, Elahi D. Pancreatic polypeptide administration enhances insulin sensitivity and reduces the insulin requirement of patients on insulin pump therapy. *J Diabetes Sci Technol*. 2011; 5:1521–28. [PubMed: 22226275]
43. Cai D, Yuan M, Frantz DF, et al. Local and systemic insulin resistance resulting from hepatic activation of IKK- β and NF- κ B. *Nat Med*. 2005; 11:183–90. [PubMed: 15685173]
44. Kiechl S, Wittmann J, Giaccari A, et al. Blockade of receptor activator of nuclear factor- κ B (RANKL) signaling improves hepatic insulin resistance and prevents development of diabetes mellitus. *Nat Med*. 2013; 19:358–63. [PubMed: 23396210]
45. Zhou X, You S. Rosiglitazone inhibits hepatic insulin resistance induced by chronic pancreatitis and IKK- β /NF- κ B expression in liver. *Pancreas*. 2014; 43:1291–98. [PubMed: 25036911]
46. Niebisz-Cielak AB, Karnafel W. Insulin sensitivity in chronic pancreatitis and features of insulin resistance syndrome. *Pol Arch Med Wewn*. 2010; 120:255–63. [PubMed: 20693955]
47. Vlasakova Z, Bartos V, Spicak J. Diabetes mellitus in chronic pancreatitis and insulin sensitivity. *Vnitr Lek*. 2002; 48:878–81. [PubMed: 16737129]

48. Yki-Jarvinen H, Kiviluoto T, Taskinen MR. Insulin resistance is a prominent feature of patients with pancreatogenic diabetes. *Metabolism*. 1986; 35:718–27. [PubMed: 3736412]
49. Nosadini R, del Prato S, Tiengo A, et al. Insulin sensitivity, binding, and kinetics in pancreatogenic and type I diabetes. *Diabetes*. 1982; 31:346–55. [PubMed: 6759250]
50. Muggeo M, Moghetti P, Faronato PP, et al. Insulin receptors on circulating blood cells from patients with pancreatogenic diabetes: a comparison with type I diabetes and normal subjects. *J Endocrinol Invest*. 1987; 10:311–19. [PubMed: 3305682]
51. Nauck M, Stockmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia*. 1986; 29:46–52. [PubMed: 3514343]
52. Knop FK, Vilsboll T, Hojberg PV, et al. The insulinotropic effect of GIP is impaired in patients with chronic pancreatitis and secondary diabetes mellitus as compared to patients with chronic pancreatitis and normal glucose tolerance. *Regul Pept*. 2007; 144:123–30. [PubMed: 17692937]
53. Vilsboll T, Knop FK, Krarup T, et al. The pathophysiology of diabetes involves a defective amplification of the late-phase insulin response to glucose by glucose-dependent insulinotropic polypeptide—regardless of etiology and phenotype. *J Clin Endocrinol Metab*. 2003; 88:4897–903. [PubMed: 14557471]
54. Hedetoft C, Sheikh SP, Larsen S, Holst JJ. Effect of glucagon-like peptide 1(7–36)amide in insulin-treated patients with diabetes mellitus secondary to chronic pancreatitis. *Pancreas*. 2000; 20:25–31. [PubMed: 10630380]
55. Knop FK, Vilsboll T, Larsen S, et al. Increased postprandial responses of GLP-1 and GIP in patients with chronic pancreatitis and steatorrhea following pancreatic enzyme substitution. *Am J Physiol Endocrinol Metab*. 2007; 292:E324–30. [PubMed: 16954337]
56. Hornum M, Pedersen JF, Larsen S, Olsen O, Holst JJ, Knop FK. Increased postprandial response of glucagon-like peptide-2 in patients with chronic pancreatitis and pancreatic exocrine insufficiency. *Pancreatology*. 2010; 10:201–17. [PubMed: 20460948]
57. Ebert R, Creutzfeldt W. Reversal of impaired GIP and insulin secretion in patients with pancreatogenic steatorrhea following enzyme substitution. *Diabetologia*. 1980; 19:198–204. [PubMed: 6997121]
58. Kuo P, Stevens JE, Russo A, et al. Gastric emptying, incretin hormone secretion, and postprandial glycemia in cystic fibrosis—effects of pancreatic enzyme supplementation. *J Clin Endocrinol Metab*. 2011; 96:E851–55. [PubMed: 21389144]
59. Perano SJ, Couper JJ, Horowitz M, et al. Pancreatic enzyme supplementation improves the incretin hormone response and attenuates postprandial glycemia in adolescents with cystic fibrosis: a randomized crossover trial. *J Clin Endocrinol Metab*. 2014; 99:2486–93. [PubMed: 24670086]
60. Rickels MR, Bellin M, Toledo FG, et al. Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: recommendations from PancreasFest 2012. *Pancreatology*. 2013; 13:336–42. [PubMed: 23890130]
61. Cui Y, Andersen DK. Pancreatogenic diabetes: special considerations for management. *Pancreatology*. 2011; 11:279–94. [PubMed: 21757968]
62. Elashoff M, Matveyenko AV, Gier B, Elashoff ZR, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology*. 2011; 141:150–56. [PubMed: 21334333]
63. Muoio DM, Newgard CB. Mechanisms of disease: molecular and metabolic mechanisms of insulin resistance and β -cell failure in type 2 diabetes. *Nat Rev Mol Cell Biol*. 2008; 9:193–205. [PubMed: 18200017]
64. Dooley J, Tian L, Schonefeldt S, et al. Genetic predisposition for β cell fragility underlies type 1 and type 2 diabetes. *Nat Genet*. 2016; 48:519–27. [PubMed: 26998692]
65. Tang H, Dong X, Hassan M, Abbruzzese JL, Li D. Body mass index and obesity- and diabetes-associated genotypes and risk for pancreatic cancer. *Cancer Epidemiol Biomarkers Prev*. 2011; 20:779–92. [PubMed: 21357378]
66. Ben Q, Xu M, Ning X, et al. Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. *Eur J Cancer*. 2011; 47:1928–37. [PubMed: 21458985]

67. Chari ST, Leibson CL, Rabe KG, Ransom J, de Andrade M, Petersen GM. Probability of pancreatic cancer following diabetes: a population-based study. *gastroenterology*. 2005; 129:504–11. [PubMed: 16083707]
68. Damiano J, Bordier L, Le Berre JP, et al. Should pancreas imaging be recommended in patients over 50 years when diabetes is discovered because of acute symptoms? *Diabetes Metab*. 2004; 30:203–07. [PubMed: 15223996]
69. Illes D, Terzin V, Holzinger G, et al. New-onset type 2 diabetes mellitus—a high-risk group suitable for the screening of pancreatic cancer? *Pancreatol*. 2016; 16:266–71. [PubMed: 26777407]
70. Ogawa Y, Tanaka M, Inoue K, et al. A prospective pancreatographic study of the prevalence of pancreatic carcinoma in patients with diabetes mellitus. *Cancer*. 2002; 94:2344–49. [PubMed: 12015758]
71. Pannala R, Leirness JB, Bamlet WR, Basu A, Petersen GM, Chari ST. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. *Gastroenterology*. 2008; 134:981–87. [PubMed: 18395079]
72. Aggarwal G, Kamada P, Chari ST. Prevalence of diabetes mellitus in pancreatic cancer compared to common cancers. *Pancreas*. 2013; 42:198–201. [PubMed: 23000893]
73. Aggarwal G, Rabe KG, Petersen GM, Chari ST. New-onset diabetes in pancreatic cancer: a study in the primary care setting. *Pancreatol*. 2012; 12:156–61. [PubMed: 22487526]
74. Pelaez-Luna M, Takahashi N, Fletcher JG, Chari ST. Resectability of presymptomatic pancreatic cancer and its relationship to onset of diabetes: a retrospective review of CT scans and fasting glucose values prior to diagnosis. *Am J Gastroenterol*. 2007; 102:2157–63. [PubMed: 17897335]
75. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer*. 2005; 92:2076–83. [PubMed: 15886696]
76. Sah RP, Nagpal SJ, Mukhopadhyay D, Chari ST. New insights into pancreatic cancer-induced paraneoplastic diabetes. *Nat Rev Gastroenterol Hepatol*. 2013; 10:423–33. [PubMed: 23528347]
77. Permert J, Ihse I, Jorfeldt L, von Schenck H, Arnqvist HJ, Larsson J. Pancreatic cancer is associated with impaired glucose metabolism. *Eur J Surg Suppl*. 1993; 159:101–07.
78. Permert J, Adrian TE, Jacobsson P, Jorfelt L, Fruin AB, Larsson J. Is profound peripheral insulin resistance in patients with pancreatic cancer caused by a tumor-associated factor? *Am J Surg*. 1993; 165:61–66. [PubMed: 8380314]
79. Chari ST, Leibson CL, Rabe KG, et al. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. *Gastroenterology*. 2008; 134:95–101. [PubMed: 18061176]
80. Chari ST, Klee GG, Miller LJ, Raimondo M, DiMagno EP. Islet amyloid polypeptide is not a satisfactory marker for detecting pancreatic cancer. *Gastroenterology*. 2001; 121:640–45. [PubMed: 11522748]
81. Gullo L, Pezzilli R, Morselli-Labate AM, Italian Pancreatic Cancer Study Group. Diabetes and the risk of pancreatic cancer. *N Engl J Med*. 1994; 331:81–84. [PubMed: 8208269]
82. Gardner TB, Hessami N, Smith KD, et al. The effect of neoadjuvant chemoradiation on pancreatic cancer-associated diabetes mellitus. *Pancreas*. 2014; 43:1018–21. [PubMed: 25000339]
83. Aggarwal G, Ramachandran V, Javeed N, et al. Adrenomedullin is upregulated in patients with pancreatic cancer and causes insulin resistance in β cells and mice. *Gastroenterology*. 2012; 143:1510–17. [PubMed: 22960655]
84. Basso D, Valerio A, Seraglia R, et al. Putative pancreatic cancer-associated diabetogenic factor: 2030 MW peptide. *Pancreas*. 2002; 24:8–14. [PubMed: 11741177]
85. Valerio A, Basso D, Brigato L, et al. Glucose metabolic alterations in isolated and perfused rat hepatocytes induced by pancreatic cancer conditioned medium: a low molecular weight factor possibly involved. *Biochem Biophys Res Commun*. 1999; 257:622–28. [PubMed: 10198261]
86. Basso D, Millino C, Greco E, et al. Altered glucose metabolism and proteolysis in pancreatic cancer cell conditioned myoblasts: searching for a gene expression pattern with a microarray analysis of 5000 skeletal muscle genes. *Gut*. 2004; 53:1159–66. [PubMed: 15247186]

87. Permert J, Ihse I, Jorfeldt L, von Schenck H, Arnquist HJ, Larsson J. Improved glucose metabolism after subtotal pancreatectomy for pancreatic cancer. *Br J Surg.* 1993; 80:1047–50. [PubMed: 8402064]
88. Permert J, Larsson J, Fruin AB, et al. Islet hormone secretion in pancreatic cancer patients with diabetes. *Pancreas.* 1997; 15:60–68. [PubMed: 9211494]
89. Chari ST, Zapiach M, Yadav D, Rizza RA. β -cell function and insulin resistance evaluated by HOMA in pancreatic cancer subjects with varying degrees of glucose intolerance. *Pancreatol.* 2005; 5:229–33. [PubMed: 15855820]
90. Permert J, Larsson J, Westermark GT, et al. Islet amyloid polypeptide in patients with pancreatic cancer and diabetes. *N Engl J Med.* 1994; 330:313–18. [PubMed: 8277951]
91. Schwarts SS, Zeidler A, Moossa AR, Kuku SF, Rubenstein AH. A prospective study of glucose tolerance, insulin, C-peptide, and glucagon responses in patients with pancreatic carcinoma. *Am J Dig Dis.* 1978; 23:1107–14. [PubMed: 367155]
92. Basso D, Plebani M, Fogar P, et al. β -cell function in pancreatic adenocarcinoma. *Pancreas.* 1994; 9:332–35. [PubMed: 8022755]
93. Fox JN, Frier BM, Armitage M, Ashby JP. Abnormal insulin secretion in carcinoma of the pancreas: response to glucagon stimulation. *Diabet Med.* 1985; 2:113–16. [PubMed: 2952394]
94. Wang F, Larsson J, Abdiu A, et al. Dissociated secretion of islet amyloid polypeptide and insulin in serum-free culture media conditioned by human pancreatic adenocarcinoma cell lines. *Int J Pancreatol.* 1997; 21:157–64. [PubMed: 9209957]
95. Sekine N, Takano K, Kimata-Hayashi N, Kadowaki T, Fujita T. Adrenomedullin inhibits insulin exocytosis via pertussis toxin-sensitive G protein-coupled mechanism. *Am J Physiol Endocrinol Metab.* 2006; 291:E9–14. [PubMed: 16760337]
96. Ramachandran V, Arumugam T, Langley R, et al. The ADMR receptor mediates the effects of adrenomedullin on pancreatic cancer cells and on cells of the tumor microenvironment. *PLoS One.* 2009; 4:e7502. [PubMed: 19847298]
97. Ramachandran V, Arumugam T, Hwang RF, Greenson JK, Simeone DM, Logsdon CD. Adrenomedullin is expressed in pancreatic cancer and stimulates cell proliferation and invasion in an autocrine manner via the adrenomedullin receptor, ADMR. *Cancer Res.* 2007; 67:2666–75. [PubMed: 17363587]
98. Keleg S, Kaye H, Jiang X, et al. Adrenomedullin is induced by hypoxia and enhances pancreatic cancer cell invasion. *Int J Cancer.* 2007; 121:21–32. [PubMed: 17290391]
99. Javeed N, Sagar G, Dutta SK, et al. Pancreatic cancer-derived exosomes cause paraneoplastic β -cell dysfunction. *Clin Cancer Res.* 2015; 21:1722–33. [PubMed: 25355928]
100. Korc M. Pancreatic cancer-associated diabetes is an “exosomopathy”. *Clin Cancer Res.* 2015; 21:1508–10. [PubMed: 25645860]
101. El-Mesallamy HO, Hamdy NM, Sallam AA. Effect of obesity and glycemic control on serum lipocalins and insulin-like growth factor axis in type 2 diabetic patients. *Acta Diabetol.* 2013; 50:679–85. [PubMed: 22307870]
102. Leung L, Radulovich N, Zhu CQ, et al. Lipocalin2 promotes invasion, tumorigenicity and gemcitabine resistance in pancreatic ductal adenocarcinoma. *PLoS One.* 2012; 7:e46677. [PubMed: 23056397]
103. Kaur S, Chakraborty S, Baine MJ, et al. Potentials of plasma NGAL and MIC-1 as biomarker(s) in the diagnosis of lethal pancreatic cancer. *PLoS One.* 2013; 8:e55171. [PubMed: 23383312]
104. Chakraborty S, Kaur S, Guha S, Batra SK. The multifaceted roles of neutrophil gelatinase associated lipocalin (NGAL) in inflammation and cancer. *Biochim Biophys Acta.* 2012; 1826:129–69. [PubMed: 22513004]
105. Chung JO, Park SY, Cho DH, Chung DJ, Chung MY. Plasma neutrophil gelatinase-associated lipocalin levels are positively associated with diabetic retinopathy in patients with type 2 diabetes. *Diabet Med.* 2016; published online April 26. doi: 10.1111/dme.13141
106. Drew BG, Hamidi H, Zhou Z, et al. Estrogen receptor (ER) α -regulated lipocalin 2 expression in adipose tissue links obesity with breast cancer progression. *J Biol Chem.* 2015; 290:5566–81. [PubMed: 25468909]

107. Catalan V, Gomez-Ambrosi J, Rodriguez A, et al. Increased adipose tissue expression of lipocalin-2 in obesity is related to inflammation and matrix metalloproteinase-2 and metalloproteinase-9 activities in humans. *J Mol Med (Berl)*. 2009; 87:803–13. [PubMed: 19466389]
108. Stolzenberg-Solomon RZ, Newton CC, Silverman DT, et al. Circulating leptin and risk of pancreatic cancer: a pooled analysis from 3 cohorts. *Am J Epidemiol*. 2015; 182:187–97. [PubMed: 26085045]
109. Gasiorowska A, Talar-Wojnarowska R, Kaczka A, Borkowska A, Czupryniak L, Malecka-Panas E. Role of adipocytokines and its correlation with endocrine pancreatic function in patients with pancreatic cancer. *Pancreatol*. 2013; 13:409–14. [PubMed: 23890140]
110. Gebhardt C, Nemeth J, Angel P, Hess J. S100A8 and S100A9 in inflammation and cancer. *Biochem Pharmacol*. 2006; 72:1622–31. [PubMed: 16846592]
111. Basso D, Greco E, Fogar P, et al. Pancreatic cancer-derived S-100A8 N-terminal peptide: a diabetes cause? *Clin Chim Acta*. 2006; 372:120–28. [PubMed: 16678810]
112. Wang WS, Liu XH, Liu LX, Jin DY, Yang PY, Wang XL. Identification of proteins implicated in the development of pancreatic cancer-associated diabetes mellitus by iTRAQ-based quantitative proteomics. *J Proteomics*. 2013; 84:52–60. [PubMed: 23571023]
113. Liou GY, Doppler H, Necela B, et al. Macrophage-secreted cytokines drive pancreatic acinar-to-ductal metaplasia through NF- κ B and MMPs. *J Cell Biol*. 2013; 202:563–77. [PubMed: 23918941]
114. Clark CE, Hingorani SR, Mick R, Combs C, Tuveson DA, Vonderheide RH. Dynamics of the immune reaction to pancreatic cancer from inception to invasion. *Cancer Res*. 2007; 67:9518–27. [PubMed: 17909062]
115. Moz S, Basso D, Padoan A, et al. Blood expression of matrix metalloproteinases 8 and 9 and of their inducers S100A8 and S100A9 supports diagnosis and prognosis of PDAC-associated diabetes mellitus. *Clin Chim Acta*. 2016; 456:24–30. [PubMed: 26923392]
116. Saren P, Welgus HG, Kovanen PT. TNF- α and IL-1 β selectively induce expression of 92-kDa gelatinase by human macrophages. *J Immunol*. 1996; 157:4159–65. [PubMed: 8892653]
117. Xu K, Geczy CL. IFN- γ and TNF regulate macrophage expression of the chemotactic S100 protein S100A8. *J Immunol*. 2000; 164:4916–23. [PubMed: 10779802]
118. Lewis AM, Varghese S, Xu H, Alexander HR. Interleukin-1 and cancer progression: the emerging role of interleukin-1 receptor antagonist as a novel therapeutic agent in cancer treatment. *J Transl Med*. 2006; 4:48. [PubMed: 17096856]
119. Hart PA, Chari ST. Diabetes mellitus and pancreatic cancer: why the association matters? *Pancreas*. 2013; 42:1207–09. [PubMed: 24152945]
120. Hart PA, Kamada P, Rabe KG, et al. Weight loss precedes cancer-specific symptoms in pancreatic cancer-associated diabetes mellitus. *Pancreas*. 2011; 40:768–72. [PubMed: 21654538]
121. Hart PA, Baichoo E, Bi Y, Hinton A, Kudva YC, Chari ST. Pancreatic polypeptide response to a mixed meal is blunted in pancreatic head cancer associated with diabetes mellitus. *Pancreatol*. 2015; 15:162–66. [PubMed: 25766398]
122. Walter U, Kohler T, Rahbari NN, Weitz J, Welsch T. Impact of preoperative diabetes on long-term survival after curative resection of pancreatic adenocarcinoma: a systematic review and meta-analysis. *Ann Surg Oncol*. 2014; 21:1082–89. [PubMed: 24322532]
123. Yuan C, Robinson DA, Qian ZR, et al. Survival among patients with pancreatic cancer and long-standing or recent-onset diabetes mellitus. *J Clin Oncol*. 2015; 33:29–35. [PubMed: 25403204]
124. Raghavan SR, Ballehaninna UK, Chamberlain RS. The impact of perioperative blood glucose levels on pancreatic cancer prognosis and surgical outcomes: an evidence-based review. *Pancreas*. 2013; 42:1210–17. [PubMed: 24152946]
125. Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology*. 2009; 137:482–88. [PubMed: 19375425]
126. Wang Z, Lai ST, Xie L, et al. Metformin is associated with reduced risk of pancreatic cancer in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Res Clin Pract*. 2014; 106:19–26. [PubMed: 24837144]

127. Singh S, Singh PP, Singh AG, Murad MH, McWilliams RR, Chari ST. Anti-diabetic medications and risk of pancreatic cancer in patients with diabetes mellitus: a systematic review and meta-analysis. *Am J Gastroenterol.* 2013; 108:510–19. [PubMed: 23399556]
128. Reni M, Dugnani E, Cereda S, et al. (Ir)relevance of metformin treatment in patients with metastatic pancreatic cancer: an open-label, randomized phase II trial. *Clin Cancer Res.* 2016; 22:1076–85. [PubMed: 26459175]
129. Kordes S, Pollak MN, Zwinderman AH, et al. Metformin in patients with advanced pancreatic cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncol.* 2015; 16:839–47. [PubMed: 26067687]
130. Andersen DK, Andren-Sandberg A, Duell EJ, et al. Pancreatitis-diabetes-pancreatic cancer: summary of an NIDDK-NCI workshop. *Pancreas.* 2013; 42:1227–37. [PubMed: 24152948]
131. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res.* 2014; 74:2913–21. [PubMed: 24840647]

Panel: Subclassifications of causes of type 3c diabetes grouped according to their potential mechanisms

Congenital or acquired complete absence of islets

- Pancreatic agenesis
- Pancreatectomy (total)

Acquired partial absence of functional islets

- Chronic pancreatitis*
- Pancreatectomy (partial)
- Severe acute pancreatitis
- Cystic fibrosis
- Haemochromatosis

Paraneoplastic

- Pancreatic ductal adenocarcinoma

Other

- Transient† hyperglycaemia of acute pancreatitis

*Includes tropical pancreatitis, which was previously referred to as fibrocalculous pancreatopathy. †Hyperglycaemia secondary to acute pancreatitis can persist for weeks.

Search strategy and selection criteria

We identified references for this Review through a search of PubMed for articles published between Jan 1, 1980, and March 1, 2016, with the following search terms: “type 3c OR pancreatogenic OR pancreatogenous OR pancreatic cancer OR pancreatic neoplasms OR pancreatitis” AND “diabetes OR diabetes mellitus”. We identified additional articles through chaining, by examining the bibliographies of these selected articles, and our own files. We included only papers published in English, and selected the final references on the basis of originality and relevance to the defined scope of this Review.

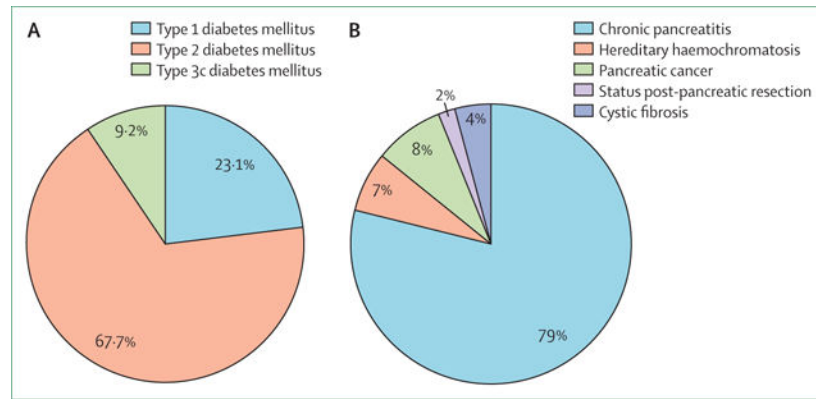


Figure. Prevalence and causes of type 3c diabetes mellitus

(A) Prevalence of type 3c diabetes in a cohort of 1868 participants with diabetes. (B) Frequency of different causes in the 117 participants with type 3c diabetes. Reproduced from Ewald and colleagues,³ by permission of John Wiley and Sons.

Table

Studies assessing the effect of PERT on incretin production and glycaemia in participants with EPI

	Ebert and Creutzfeldt 1980⁵⁷	Knop and colleagues 2007⁵⁵	Kuo and colleagues 2011⁵⁸	Perano and colleagues 2014⁵⁹
Disease state	Chronic pancreatitis with EPI	Chronic pancreatitis with EPI	Cystic fibrosis with EPI	Cystic fibrosis with EPI
Glycaemic status of cases (n)	IGT (16)	DM (4), IGT (3), normal (1)	IGT (1), normal (4)	DM (2), normal (12)
Glycaemic status of controls (n)	Normal (14)	Normal (8)	Normal (6)	Normal (7)
Weight or BMI (cases vs controls)	59.7 vs 62 kg	21 vs 23 kg/m ²	20 vs 21.3 kg/m ²	BMI Z scores: 0.12 vs 0.2
Mean age (cases vs controls; years)	40 vs 17	57 vs 58	253.8 vs 21.7	13.1 vs 14.6
Meal	Liquid mixed meal	Liquid mixed meal	Mashed potatoes with olive oil	High fat pancake
Meal composition (% calories of fat/carbohydrates/protein)	26%/60%/14%	27.7%/58%/9.5%	61%/39%/0%	75%/25%/0%
Dose of lipase administered in PERT	N/A *	50000 U	100000 U	50 000 IU
Effect of PERT on postprandial AUC				
Total GLP-1	N/A	↑	↔/↑	↑
Total GIP	↑	↑	↑	↑
Insulin	↑	↑	↔	↔
Glucose	↓	↔	↓	↓
Glucagon	N/A	↑	↔/↑	↑

EPI=exocrine pancreatic insufficiency. IGT=impaired glucose tolerance. DM=diabetes mellitus. BMI=body-mass index. PERT=pancreatic enzyme replacement therapy. AUC=area under the curve. GLP-1=glucagon-like peptide-1. N/A=not available. GIP=glucose-dependent insulintropic polypepti. ↑ increased. ↔ no change. ↓ decreased.

* Participants were given 9 g of pancreatin before the study; however, the exact dose of lipase administered was not available.