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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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See Online for appendix

Contributors

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Declaration of interests

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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 pancreatopathy[7]). 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 Bretzel[9] 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 homoeostasis 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 1β, tumour necrosis factor (TNF) α, and interferon γ, has been demonstrated.[30] Islets expressing high concentrations of interleukin 1R and interleukin 1β induce β-cell apoptosis.[31] Clinical studies of antagonists to interleukin 1R, interleukin 1β, and TNFα 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-κB kinase-β and NF-κB.[43] Blockade of NF-κB 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 insulinotropic 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 homoeostasis

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 (HbA_{1c} <8% or <64 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 colleagues[66] 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 homoeostatic 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 TNFα and interleukin 1β— 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 homoeostasis, 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 predis positions 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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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.

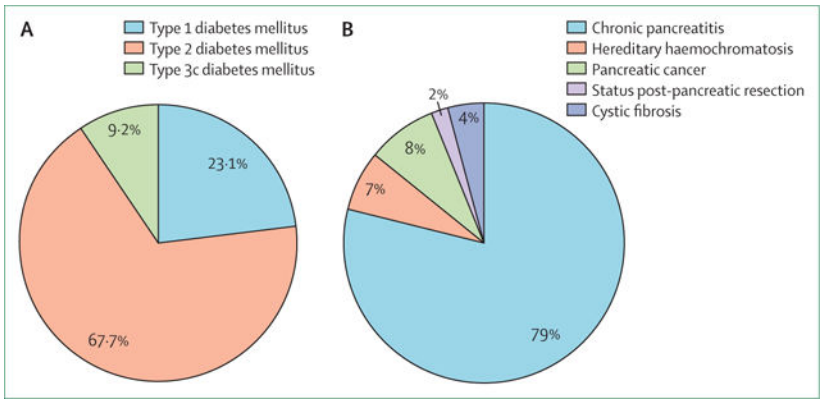

Figure. Prevalence and causes of type 3c diabetes mellitus

(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 1980[57]	**Knop and colleagues 2007[55]**	**Kuo and colleagues 2011[58]**	**Perano and colleagues 2014[59]**
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%	6l%/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 insulinotropic polypepti. ↑ ncreased. ↔ no change. ↓ecreased.

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