DIAGNOSIS OF ENDOCRINE DISEASE

Diagnosing and classifying diabetes in diseases of the exocrine pancreas

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Abstract

Diabetes in the setting of diseases of the exocrine pancreas has long existed as a known, but underdiagnosed or misdiagnosed, disorder. It currently finds itself in a state of taxonomic dereliction and requires a long overdue refurbishment. Correct conceptualisation is a key precondition for knowledge development in this disorder. This article lays out the epistemological foundation for diabetes of the exocrine pancreas (DEP) and presents a synthesis of the current interdisciplinary discourse on diagnosing and classifying DEP. A diagnosis of DEP in people with no medical records of pre-existing diabetes is generally based on the most up-to-date biochemical criteria endorsed by the American Diabetes Association and European Association for the Study of Diabetes. The presence of exocrine pancreatic dysfunction is not considered a mandatory diagnostic criterion for DEP but is rather a significant risk factor for developing DEP. DEP principally comprises post-pancreatitis diabetes mellitus, pancreatic cancer-related diabetes, and cystic fibrosis-related diabetes, which are mutually exclusive with autoimmune diabetes and type 2 diabetes. Other exclusions and stipulations apply. The DEP criteria will be instrumental in aiding optimal design and conduct of clinical studies, uniform collection of health utilisation data, meaningful comparison of scientific findings across countries, and clear communication among stakeholders (healthcare providers, patients, medical regulatory authorities, pharmaceutical industry).

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Introduction

The pancreas is composed of functionally diverse exocrine and endocrine compartments that uniquely originate from a common progenitor. One facet of the predetermined interplay between the exocrine and endocrine pancreas is the development of diabetes in diseases of the exocrine pancreas. Although dwarfed by type 2 diabetes, this type of diabetes is the second most common type of new-onset diabetes in adults (surpassing type 1 diabetes) (1). Its prevalence has nearly tripled in the past decade and its incidence is projected to have a 2.8% annual growth and reach 15.8 per 100 000 general population in 2050 (2, 3). Further, it is a valid taxon in its own right as diabetes in diseases of the exocrine pancreas

is different from type 2 diabetes in many regards. It is associated with significantly worse short-term outcomes such as blood glucose control and glycaemic variability in the first few years after the diagnosis of diabetes (1, 4). It is associated with significantly worse long-term outcomes such as death from any cause in general and cancer mortality in particular (5, 6). It has a unique response to common anti-diabetic medications (7, 8). Last, data on distinct pathophysiological signatures in this type of diabetes have emerged (9, 10, 11, 12).

Although a wealth of knowledge on diabetes in diseases of the exocrine pancreas has been accumulated, classification of this type of diabetes has not kept pace.

The 2019 clinical practice guidelines on diagnosis and classification of diabetes issued by major professional bodies merely include a 100-odd words text under the section ‘other specific types of diabetes’ that has hardly changed since the 1990s (13, 14, 15, 16). It would appear that, in more than half a century since the publication of the first classification of diabetes by the World Health Organization (17), there has been no progress in regards to the framework for classifying diabetes in diseases of the exocrine pancreas. Also, it was not until 2017 that the first guidelines by a major professional body in the field of gastroenterology (United European Gastroenterology) formally assessed the body of evidence on diabetes in diseases of the exocrine pancreas (18). These have made diabetes in diseases of the exocrine pancreas nosologically derelict. Diseases of the exocrine pancreas typically have a complex aetiology and pathogenesis that cannot be encapsulated by a single feature (19, 20), and so is the diabetes that follows them. A modern classification system that defines fairly homogenous patient groups in a hierarchical fashion is essential to facilitate communication between key stakeholders and promote standardisation for reporting research findings (to compare them impartially across studies, geographic regions, and time periods). This is especially important for diabetes in diseases of the exocrine pancreas because of the highly interdisciplinary nature of management of this type of diabetes and research into it, involving endocrinologists, gastroenterologists, surgeons, oncologists, primary care physicians, nurses, dieticians, radiologists, and other healthcare professionals. Also, the absence of a standardised nomenclature puts diabetes in diseases of the exocrine pancreas in a catch-22 situation: major professional bodies in the field cannot recommend optimal treatments for these people without evidence from well-designed randomised controlled trials whereas pharmaceutical companies are hesitant to be involved in the trials of diseases without distinct names and frameworks.

Semantic evolution

The notion of diabetes in diseases of the exocrine pancreas has undergone a long evolution and, in parallel with the evolution, its meaning has also changed over time. The initial terms stemmed from surgical explorations of the pancreas. In 1892, Harley coined the term ‘pancreatic diabetes’ to denote the development of diabetes in animals after the removal of the pancreas (21). It was followed by

the term ‘pancreoprivic diabetes’ in the 1950s – to denote the development of diabetes following a complete removal of the entire pancreas, and the term ‘pancreatogenic diabetes’ in the 1960s (as an adoption of the earlier term ‘pancreatogenic steatorrhea’) – to denote the development of diabetes following pancreaticoduodenectomy (which started to become widely used by surgeons at the time) (22, 23). Although these terms were initially useful as they put diabetes secondary to an insult to the pancreas into a separate category, these are rather anachronisms as nowadays it is well established that, with very rare exceptions, the development and progression of diabetes involve dysfunction of the islets of Langerhans in the pancreas. This means that virtually any type of diabetes is ‘pancreatic’ or ‘pancreatogenic’, at least to some extent. Given that the Latin verb *privo* means ‘to deprive’, the term ‘pancreoprivic diabetes’ is not specific enough as it is now recognised that people with not only diabetes secondary to diseases of the exocrine pancreas but also type 1 diabetes and type 2 diabetes may have ‘deprived’ exocrine pancreatic function (24, 25). Overall, vacillating between the above terms is counter-productive.

The next stage in the semantic evolution of the notion of diabetes in diseases of the exocrine pancreas was the use of the misnomer ‘type 3c diabetes’. The oft-cited refrain that this term is endorsed by the World Health Organization and by the American Diabetes Association has been perpetuated by several published reviews on the topic as well as countless webpages. However, the sobering truth is that neither the 2019 classification of diabetes by the World Health Organization nor its earlier versions has ever designated a distinct term for diabetes in diseases of the exocrine pancreas (13, 14). Diabetes in diseases of the exocrine pancreas has invariably been under ‘other specific types of diabetes’ and, hence, has always been semantically indistinguishable from entities such as monogenic diabetes, drug-induced diabetes, or infection-related diabetes. Similarly, neither the 2019 classification of diabetes by the American Diabetes Association nor its earlier versions (annual updates since 1989) have ever encouraged the use of the term ‘type 3c diabetes’ (15, 16). Actually, the term ‘type 3 diabetes’ was coined and promulgated in 2006–2008 by a group of US neuroscientists who observed some brain-specific perturbations in insulin signalling mechanisms and formed a belief that Alzheimer’s disease represents a new distinct type of diabetes (dubbed ‘type 3 diabetes’) that selectively involves the brain (26, 27). While the notion of diabetes of the brain never got recognised by any professional body in the field of diabetology or neurology,

it did attract the attention of a group of German internists interested in the use of faecal elastase-1 test (then only recently marketed) in type 1 and type 2 diabetes. In 2008, the group introduced the term ‘type 3c diabetes’ in the (non-peer-reviewed) proceedings of two small industry-sponsored conferences/workshops (28, 29). The authors believed that a document published by the American Diabetes Association a decade earlier (specifically, the 1998 report of the expert committee on the diagnosis and classification of diabetes mellitus (16)) had assigned a new label (i.e. ‘3c’ – note the Arabic numeral) to ‘pancreatic diseases with exocrine dysfunction as a cause for diabetes’ (28). However, the text of the 1998 document (or, for that matter, any guideline by the American Diabetes Association between 1999 and 2008) did not contain any reference to ‘type 3c’ or exocrine dysfunction (16).

The confusion might have arisen from a new table outlining the aetiological classification of diabetes published in the 1998 document (and subsequently re-published with minor updates not related to diseases of the exocrine pancreas in the 2014 document) (16, 30). The table used the Roman numerals I-IV, which were not meant to be interpreted as designations of distinct types of diabetes. ‘Other specific types of diabetes’ happened to be presented under the Roman numeral III (whereas, for example, gestational diabetes was presented under the Roman numeral IV). Further, under section III, diseases of the exocrine pancreas happened to be presented under the letter ‘C’ (whereas, for example, drug-induced diabetes was presented under the letter ‘E’ and infection-related diabetes – under the letter ‘F’).

The latest stage in the semantic evolution of the notion was the introduction of ‘diabetes of the exocrine pancreas’, memorably and distinctly acronymised to DEP, in 2017 (31). The term has been increasingly used since then (1, 32, 33, 34, 35). Accumulating evidence shows that excessive intra-pancreatic fat deposition (located externally to the islets of Langerhans) plays a key role in the pathogenesis of diabetes secondary to pancreatitis, pancreatic cancer, and cystic fibrosis, but not in the pathogenesis of type 1 diabetes or type 2 diabetes (36, 37, 38, 39, 40, 41). Hence, it is pathophysiologically meaningful and semantically accurate to call this type of diabetes as one of the exocrine pancreas. It is important to acknowledge that the mechanisms that underlie diabetes in mild acute pancreatitis, end-stage chronic pancreatitis, pancreatic cancer, and cystic fibrosis are not the same (10, 12, 19). For these disorders to stand a chance of occupying a distinct niche (as is, for example, the case for gestational diabetes mellitus) in future revisions of classifications of

diabetes mellitus by major professional bodies, the lexicon used by the stakeholders in the field should be linguistically aligned with the terminology already endorsed by those bodies for other entities representing secondary diabetes. In particular, the term ‘post-transplantation diabetes mellitus’ is deeply ingrained in the lexicon of both endocrinologists and surgeons to describe diabetes secondary to transplantation (15). Hence, newly diagnosed diabetes mellitus in the post-pancreatitis setting is best to be termed ‘post-pancreatitis diabetes mellitus’ (PPDM). This term is considered superior to the term ‘pancreatitis-related diabetes’ and such like because the latter does not semantically rule out prevalent diabetes, which can (and should) be readily done, especially in people with a history of acute pancreatitis. The term ‘cystic fibrosis-related diabetes’ (CFRD) is semantically accurate, already widely used, and should remain a part of the terminology (15). For the purpose of consistency, diabetes associated with pancreatic cancer – a disorder in which it is often uneasy to rule out prevalent diabetes – is best to be termed ‘pancreatic cancer-related diabetes’ (PCRD). Most importantly, DEP is not merely a new umbrella term that replaces the old ones. Unlike the amorphous (and, at times, baseless) terms used in the past, DEP is a term that denotes a clearly defined, uniform, and succinct set of entities that are under the scope, therefore unequivocally distinguishing DEP from other types of diabetes.

Core entities

The core entities that makeup DEP are PPDM, PCRD, and CFRD (Table 1). Given that there are two main types of pancreatitis (acute pancreatitis and chronic pancreatitis), post-acute pancreatitis diabetes mellitus and post-chronic pancreatitis diabetes mellitus are recognised – acronymised to PPDM-A and PPDM-C, correspondingly. A series of careful histopathological studies conducted in the early 1990s and more recent meta-analysis of clinical studies have established that pancreatitis often represents a disease continuum (42, 43). While the first attack of acute pancreatitis and end-stage chronic pancreatitis are typically diagnosed in a straightforward manner, identifying individuals who transition between the two states is clinically challenge (44). Historically, attempts to characterise an intermediate state have alternated between terms such as ‘possible’, ‘probable’, and ‘early’ chronic pancreatitis. Recent high-quality MRI studies have suggested that relatively simple measurements such as total pancreas volume (that can potentially be

Table 1 Classification of diabetes of the exocrine pancreas.**General inclusions**

- Post-pancreatitis diabetes mellitus (PPDM)
- Post-acute pancreatitis diabetes mellitus (PPDM-A)
- Post-chronic pancreatitis diabetes mellitus (PPDM-C)
- Pancreatic cancer-related diabetes (PCRD)
- Cystic fibrosis-related diabetes (CFRD)

General exclusions

- Stress hyperglycaemia
- Autoimmune diabetes with first recognition after an attack of pancreatitis
- Diabetes with first recognition during pregnancy after an attack of pancreatitis
- Maturity-onset diabetes of the young
- Drug-induced diabetes
- Diabetes after pancreatic surgery
- Diabetes after blunt pancreatic (abdominal) trauma
- Diabetes secondary to pancreatic agenesis/hypoplasia
- Diabetes secondary to hereditary hemochromatosis

Special entities

- Antecedent diabetes mellitus in pancreatitis (ADMP)
- New-onset diabetes in pre-symptomatic pancreatic ductal adenocarcinoma (NOD-PDAC)

automated and the power of artificial intelligence can be leveraged) could serve the purpose (45, 46, 47, 48). However, until age- and sex-specific thresholds for them are determined and validated, chronic pancreatitis should be diagnosed only in the presence of the following changes in the pancreas: intraductal and/or parenchymal pancreatic calcifications on CT or MRI and/or radiological evidence of strictures and dilatations in side branches and/or the main pancreatic duct on magnetic resonance cholangiopancreatography (Cambridge grade 3 or 4) and/or histological proof of chronic pancreatitis from biopsy samples undertaken by endoscopic ultrasonography or from a surgically resected specimen (18, 49). The implication for PPDM is that individuals with diabetes following an attack of pancreatitis, which did not lead to the above morphological changes, should be labelled as PPDM-A. People who develop diabetes as a sequela of disconnected pancreatic duct syndrome should be labelled as PPDM-A as the syndrome is typically a complication of acute necrotising pancreatitis (50, 51). Entities such as hereditary pancreatitis, tropical calcific pancreatitis, and autoimmune pancreatitis are typically considered subtypes of chronic pancreatitis. There are reports in the literature of diabetes associated with hereditary pancreatitis, tropical pancreatitis (also known as fibrocalculous pancreatopathy or fibrocalculous pancreatic diabetes), and autoimmune pancreatitis (52, 53, 54, 55, 56, 57). Until further evidence on the burden and distinct features of these rather rare disorders accumulates, they should be labelled as PPDM-C

(unless the exclusion criteria or stipulations described below and presented in Table 1 are met).

In people with no medical records of diabetes (i.e. known diagnosis and/or use of antidiabetic medications for the purpose of treating diabetes), the biochemical diagnostic criteria for diabetes outlined in the American Diabetes Association guidelines should generally be used for diagnosing DEP (Table 2). However, fasting plasma glucose (or random glucose for that matter) should not be used for the purpose of diagnosing PPDM during the course of pancreatitis (and, arbitrarily, within 90 days after hospitalisation) as its elevated levels may reflect the acute stress response and may also be a consequence of management of pancreatitis (e.g. parenteral nutrition, intravenous infusion of dextrose). Specifically, fasting plasma glucose measured in outpatient setting only (but not in the emergency department, urgent care, or inpatient setting) should be acceptable. In a clinical setting, glycated haemoglobin and/or fasting plasma glucose are often preferred to oral glucose tolerance test because of ease of use, convenience, and acceptability to patients. However, in a research setting, the use of oral glucose tolerance test may, in theory, enable an earlier diagnosing of PPDM as the test neither is confounded by the acute stress response (as is the case with fasting plasma glucose) nor requires the 90-day lag period (as is the case with glycated haemoglobin). A 2020 case-control study of 52 people from Ireland suggested that oral glucose tolerance test may be beneficial in diagnosing PPDM-A, though its findings are inconclusive because of the rather liberal inclusion criteria for diabetes and overly restrictive criteria for pancreatitis (33). Oral glucose tolerance test is also currently considered to be a more suitable diagnostic test for CFRD as earlier studies questioned the validity of glycated haemoglobin in this setting (15, 58). It is important to underscore that glycated haemoglobin should be measured using a method certified by the National Glycohaemoglobin Standardisation Program and standardised to the Diabetes Control and Complications Trial reference assay. In addition to standardisation and comparability between different studies, this ensures a proper separation of glycated haemoglobin from other glycohaemoglobins (that are chemically distinct moieties produced by the binding of glucose and other carbohydrates to various sites on haemoglobin) (59). Both glycated haemoglobin and fasting plasma glucose should be measured on fresh, never frozen sample. The use of point-of-care devices should be discouraged as it may result in a considerable misclassification bias (60).

Table 2 Diagnostic criteria for diabetes in individuals with a history of pancreatitis based on laboratory workup. In the absence of unequivocal hyperglycaemia, diagnosis requires two abnormal test results on simultaneous or consecutive testing. Fasting refers to no calorie intake for at least 8 h. 'Not available' refers to both missing and inconclusive (due to chronic disorders interfering with the accuracy of measurements) values.

	Timing of diabetes workup in relation to the first attack of pancreatitis				
	Before		During or within 90 days		More than 90 days
Type 2 diabetes	HbA1c ≥ 48 mmol/mol (6.5%) OR FPG ≥ 7.0 mmol/L (126 mg/dL)	AND/OR	HbA1c ≥ 48 mmol/mol (6.5%)	AND	Any HbA1c/FPG
PPDM	HbA1c AND/OR FPG not available	AND	HbA1c not available	AND	HbA1c ≥ 48 mmol/mol (6.5%) AND/OR FPG ≥ 7.0 mmol/L (126 mg/dL)
NODAP	HbA1c < 48 mmol/mol (6.5%) AND FPG < 7.0 mmol/L (126 mg/dL)	AND/OR	HbA1c < 48 mmol/mol (6.5%)	AND	HbA1c ≥ 48 mmol/mol (6.5%) AND/OR FPG ≥ 7.0 mmol/L (126 mg/dL)

FPG, fasting plasma glucose; NODAP, new-onset diabetes after pancreatitis; PPDM, post-pancreatitis diabetes mellitus.

Exocrine pancreatic dysfunction should not be used as a diagnostic criterion for DEP as it is not a specific characteristic of PPDM or PCRD. Exocrine pancreatic dysfunction often develops in people with type 1 and type 2 diabetes (including those requiring insulin therapy). This was first demonstrated in several histopathological studies and then confirmed in 3 meta-analyses of more than 80 clinical studies that employed either direct/indirect pancreatic function tests or pancreas volumetry (25, 61, 62, 63). Almost invariably, those people had no history of diseases of the exocrine pancreas. However, it is acknowledged that exocrine pancreatic dysfunction also often develops in people with diseases of the exocrine pancreas (24, 64). A 2020 cohort study of 9124 individuals with acute or chronic pancreatitis from New Zealand showed that those with exocrine pancreatic dysfunction secondary to pancreatitis had a significantly higher risk for PPDM (adjusted hazard ratio 3.83; $P < 0.05$) (65). Type of pancreatitis (acute vs chronic) and characteristics of acute pancreatitis (aetiology, severity, recurrence) did not materially affect the association. Based on the above arguments, exocrine pancreatic dysfunction should be viewed as a strong risk factor for DEP but not its defining characteristic.

Although the underlying disease of the exocrine pancreas should be diagnosed in line with current standards of practice for each disease (18, 49), it is pertinent to note that evidence of pathological pancreatic imaging (by MRI, CT, or endoscopic ultrasound) in itself is not required as a diagnostic criterion for DEP. This is because some people with diabetes and diseases of the exocrine pancreas may have visually unremarkable imaging of the pancreas (66). For example, PCRD can be suspected in people with diabetes who have unintentional

weight loss, anorexia, jaundice, elevated serum CA 19–9 level and normal pancreatic imaging. It was shown that new-onset diabetes not infrequently manifests before cancer becomes visible on cross-sectional imaging (67). Further, the degree of hyperglycaemia is significantly associated with pancreatic tumour volume and grade (68). But the largest fraction of people with normal pancreatic imaging is those with PPDM following mild (non-necrotising) pancreatitis. While the old dogma postulated that extensive structural damage of the islets of Langerhans is mandatory for the development of PPDM, a series of modern meta-analyses, population-based studies, and prospective longitudinal cohort studies, has established that individuals after mild (non-necrotising) acute pancreatitis are also at a high risk of developing PPDM (69, 70, 71, 72). These people typically have visually unremarkable imaging of the pancreas at the time of diabetes diagnosis (73, 74, 75, 76, 77). Last but not least, given that diseases of the exocrine pancreas are ubiquitous, the reliance on MRI, CT, or endoscopic ultrasound would make it virtually unfeasible to diagnose DEP outside high-income countries.

Special entities

Two diabetes entities in disease of the exocrine pancreas can be recognised only retrospectively (Table 1). It is important to be aware of them as they are not infrequently reported in clinical studies. The first entity is new-onset diabetes in pre-symptomatic pancreatic ductal adenocarcinoma (NOD-PDAC). A growing body of literature indicates that new-onset diabetes is a promising early marker in pre-symptomatic pancreatic cancer (especially if accompanied

by change in body composition) (68, 78, 79). Importantly, it was shown that exocrine pancreatic dysfunction is a driver of adipose tissue loss in early pancreatic ductal adenocarcinoma (80). Given that pancreatic enzyme supplementation paradoxically led to worse survival in mice, it was hypothesised that peripheral tissue loss in early-stage and cachexia in late-stage pancreatic ductal adenocarcinoma represent distinct phenomena. Of note, NOD-PDAC may overlap with PPDM in some people. A 2020 population-based study of 139 843 individuals from New Zealand showed that individuals with PPDM had a significantly higher risk of pancreatic cancer than those with type 2 diabetes and no history of pancreatitis (adjusted hazard ratio 6.94; $P < 0.05$) (6). The observed magnitude of risk was similar to that for families with a history of pancreatic cancer and inherited genetic mutations in pancreatic cancer predisposition genes, which suggests that future studies on early detection of pancreatic cancer may benefit from taking into account the occurrence of PPDM in study populations.

The second entity is diabetes (of any recognised type) that predates the diagnosis of pancreatitis, which we term 'antecedent diabetes mellitus in pancreatitis' (ADMP) (Fig. 1). One scenario is a significantly increased risk of developing pancreatitis and worse in-hospital outcomes of pancreatitis in people with pre-existing diabetes (81, 82). A specific example is severe hypertriglyceridaemia-induced acute pancreatitis in people with diabetes, which may (or may not) relate to diabetic ketoacidosis (83, 84, 85). People with lipodystrophy – a heterogeneous group of genetic or acquired disorders characterised by absence or loss of subcutaneous fat – may also have ADMP. Given that these people often have marked insulin resistance, they are at high risk of developing diabetes mellitus. People with lipodystrophy also often have severe hypertriglyceridaemia, which puts them at high risk of developing acute pancreatitis. People with co-existing diagnoses of lipodystrophy, diabetes, and hypertriglyceridaemia-induced acute pancreatitis should be labelled as either ADMP or PPDM depending on whether or not diabetes predates the diagnosis of pancreatitis. Of note, a 2018 study showed that familial partial lipodystrophy is characterised by excess intra-pancreatic fat deposition (robustly determined with the use of chemical shift-encoded MRI) (86). Further investigations of this group of people could provide valuable insights into the intricate interplay between the endocrine and exocrine pancreas.

Similar to people with lipodystrophy, people with type 1 autoimmune pancreatitis – a benign IgG4-related

Figure 1

Terminology for diabetes in the setting of pancreatitis. Diabetes with first recognition prior to the first attack of pancreatitis is deemed ADMP. This entity may include diagnosed diabetes of any type, although most commonly it is type 2 diabetes. Diabetes with first recognition during follow-up of individuals with pancreatitis is deemed PPDM (unless the general exclusions (Table 1) are met). Because diabetes may remain undiagnosed prior to and during hospitalisation for pancreatitis (i.e. at baseline), the term 'new-onset diabetes after pancreatitis' (NODAP) is adopted to describe individuals with PPDM who had documented absence of diabetes at baseline (as evidenced by available glycated haemoglobin and/or fasting plasma glucose data). Given that prediabetes is known as one of the strongest risk factors for diabetes, the term 'new-onset prediabetes after pancreatitis' (NOPAP) is also adopted to describe individuals with pancreatitis and prediabetes during follow-up who had documented euglycaemia at baseline (as evidenced by available glycated haemoglobin and/or fasting plasma glucose data). ADMP, antecedent diabetes mellitus in pancreatitis; NODAP, new-onset diabetes after pancreatitis; PPDM, post-pancreatitis diabetes mellitus.

digestive disease that may masquerade as pancreatic ductal adenocarcinoma (55, 87) – and diabetes (in the absence of islet-directed autoantibodies) may have ADMP or PPDM depending on whether or not diabetes predates the diagnosis of pancreatitis. The additional facet of complexity in this group of people is that they may require the administration of large doses of corticosteroids (as the most effective treatment for autoimmune pancreatitis), which may lead to new-onset diabetes (87). In that case, diabetes should be labelled as drug-induced diabetes. Another scenario is ketosis-prone diabetes, where individuals presenting with diabetic ketoacidosis and negative autoimmune markers initially require insulin therapy but then become insulin-independent (88). These

people can be recognised only retrospectively based on the need for long-term insulin therapy and they may have an attack of pancreatitis at any time after onset of diabetes. The last scenario worth noting here is when metabolic traits of individuals with classical uncomplicated type 2 diabetes worsen following an attack of pancreatitis (e.g. need for insulin, development of exocrine pancreatic dysfunction, skeletal muscle loss) (69, 76).

Key exclusions

The intents of diagnostic criteria and classification criteria are not the same (89). Diagnostic criteria are broad and must reflect the different traits of diabetes (i.e. its heterogeneity), with a primary intent of accurately identifying as many individuals with the disease as possible. That is why the diagnostic criteria for diabetes by the American Diabetes Association are advocated in the present discourse (Table 2). Classification criteria are standardised definitions, used with a primary intent of creating relatively homogeneous well-defined cohorts of patients for clinical or population-based research. They are not meant to capture the entire universe of possible patients but rather to group together the majority of patients who share key features of the subtypes of diabetes in question. That is why DEP and other types of diabetes are viewed as mutually exclusive, resulting in several diabetes entities being considered not to be part of the DEP criteria (Table 1).

The presence of several entities characterised by hyperglycaemia in people with pancreatitis rules out the diagnosis of PPDM as an operational means of producing the most cleanly defined PPDM group (Fig. 2). Specifically, the presence of autoimmune markers diagnostic for type 1 diabetes (i.e. islet cell antibody or antibodies to glutamic acid decarboxylase, insulin, tyrosine phosphatase-like proteins, or zinc transporter-8) rules out the diagnosis of PPDM. Also, autoimmune markers are often (but not always) present in patients treated with monoclonal antibodies that block immune inhibitory ligands CTLA-4 and PD-1 (known as checkpoint inhibitors) (90). It was reported that around 1% of patients who receive this modern treatment for cancers resistant to conventional cancer therapies develop fulminant diabetes (91). Of them, 42% have markedly elevated lipase, amylase and/or imaging findings suggestive of acute pancreatitis at the time of diabetes diagnosis (91). This form of diabetes should be considered as part of drug-induced diabetes – a type of secondary diabetes recognised by the American Diabetes Association (15). Also, stress hyperglycaemia

during pancreatitis (or up to 90 days after pancreatitis) rules out the diagnosis of PPDM (81, 92). The 90-day lag period is applied because levels of glycated haemoglobin reflect average plasma glucose concentration over the preceding 8–12 weeks. While identifying transient stress hyperglycaemia during the course of pancreatitis is important, stress hyperglycaemia occurs in up to 7 out of 10 patients with pancreatitis and indiscriminately labelling the majority of pancreatitis patients during hospitalisation (or shortly after it) with PPDM would not be helpful (93, 94). This was shown in a 2015 population-based study of 14 830 people from Taiwan when disregarding the 90-day lag period in people with acute pancreatitis resulted in the marked inflation of incidence density of diabetes from 22.5 to 60.8 per 1000 person-years (70). At the same time, incidence density of diabetes in controls from the general population (who had no prior diagnosis of diabetes or disease of the exocrine pancreas) did not change considerably: from 6.7 to 8.0 per 1000 person-years (70).

It is well recognised that pancreatic surgery is associated with an increased risk of diabetes. A 2015 systematic review of 26 clinical studies (encompassing 1731 patients after pancreatic resection) showed that as many as 2 out of 5 patients during follow-up developed postoperative diabetes (95). However, postoperative changes in glucose metabolism are often due to not surgery but pre-existing disease(s). Several studies demonstrated that the development of diabetes was not significantly associated with the type of pancreatic resection performed (pancreaticoduodenectomy vs distal pancreatectomy) (96, 97) or the volume of pancreas resected (98, 99, 100, 101). Further, a 2015 population-based study of 3914 preoperative patients without diabetes from Taiwan showed that pancreatitis was the only pre-existing disease significantly associated with the development of diabetes after pancreatic resection (odds ratio 1.4; $P = 0.002$) (102). Similarly, a 2017 population-based study of 678 preoperative patients without diabetes from the USA showed that the only independent predictors of diabetes after pancreatic resection were pancreatitis (hazard ratio 1.5; $P = 0.03$) and Charlson comorbidity index (hazard ratio 1.6; $P = 0.02$) (97). Given that the most common indications for pancreatic resection are pancreatitis and pancreatic cancer (i.e. the core entities in the DEP criteria), inclusion of postoperative diabetes as a part of DEP would result in a logical fallacy called *circulus in probando* and, therefore, would artificially inflate the epidemiological estimates of DEP. A rare indication for pancreatic resection is blunt pancreatic trauma. Contrary to earlier anecdotal

Figure 2

Diagnostic algorithm to identify post-pancreatitis diabetes mellitus. Markers of the autoimmune process refer to antibodies to the cytoplasm of islet cells, insulin, glutamic acid decarboxylase, insulinoma-associated antigen-2, and zinc transporter-8. The 90-day lag period is arbitrary and some individuals after pancreatitis may, in theory, develop new-onset diabetes sooner than that. However, the clinical importance of establishing a diagnosis of chronic disease such as diabetes earlier than 90 days is not obvious. HbA1c, glycated haemoglobin; FPG, fasting plasma glucose.

case reports, a 2017 cohort study showed that pancreatic trauma did not lead to new-onset diabetes within 3 years of injury (103).

Diabetes secondary to pancreatic agenesis (or hypoplasia) is also considered not to be part of the DEP criteria. Pancreatic agenesis is a very rare congenital malformation of the pancreas. In people with this malformation, diabetes occurs almost invariably under 6 months of age and is often linked to heterozygous mutations in the transcription factor *GATA6* (104, 105, 106). Therefore, it should be considered as part of neonatal diabetes – a subtype of monogenic diabetes recognised by the American Diabetes Association (15). Another example of monogenic diabetes is type 8 maturity-onset diabetes of the young, characterised by exocrine pancreatic dysfunction and caused by heterozygous mutations in carboxyl-ester lipase – one of the four lipases expressed in pancreatic acini (107). However, the enzyme is not pancreas-specific: it is also expressed in lactating mammary glands in humans and is secreted with the milk (107). In

addition, genetic disease that is not part of the DEP criteria is hereditary hemochromatosis. It is caused by mutations of a number of genes involved in the hepcidin-ferroportin axis and is characterised by an unregulated intestinal iron absorption and increased iron deposition in several organs (including but not limited to the pancreas). The prevalence of diabetes in hereditary hemochromatosis is around 20% but there is no consensus in the literature on what type of diabetes it is (108). A large 2001 study from Denmark showed that more people with late-onset type 1 diabetes than controls from the general population (1.26% vs 0.25%) were homozygous for C282Y – the most common mutation in type 1 hereditary hemochromatosis (109). Given that hereditary hemochromatosis can lead to dysfunction of not only the pancreas but also other key organs involved in the pathogenesis of diabetes (such as the liver, skeletal muscle, gut, brain), there is no sufficient scientific evidence to consider diabetes secondary to hereditary hemochromatosis as part of DEP. It is worth noting though that secondary alteration in iron

Table 3 Key terms and abbreviations (in alphabetical order).

Abbreviation	Term
ADMP	Antecedent diabetes mellitus in pancreatitis
CFRD	Cystic fibrosis-related diabetes
DEP	Diabetes of the exocrine pancreas
NODAP	New-onset diabetes after pancreatitis
NOD-PDAC	New-onset diabetes in pre-symptomatic pancreatic ductal adenocarcinoma
NOPAP	New-onset prediabetes after pancreatitis
PCRD	Pancreatic cancer-related diabetes
PPDM	Post-pancreatitis diabetes mellitus
PPDM-A	Post-acute pancreatitis diabetes mellitus
PPDM-C	Post-chronic pancreatitis diabetes mellitus

metabolism – unrelated to one of the genetic mutations leading to type 1–4 hereditary hemochromatosis – can be a characteristic of DEP, in particular PPDM (110, 111, 112).

Conclusion

The National Academy of Medicine (USA) links the provision of quality health care to a diagnostic process that is both timely and accurate (113). This is far from being the case for DEP because it is typically diagnosed late and often misdiagnosed as type 2 diabetes (and sometimes as type 1 diabetes) (1). Given that DEP is characterised by a significantly poorer glycaemic control in the first few years after the diagnosis in comparison with type 2 diabetes and taking into account the well-known legacy effect of early glycaemic control on micro- and macro-vascular complications and death, it is important to raise the awareness and early recognition of DEP (114). This underscores the need to offer appropriate management early in the course of DEP with a view to achieving near-normal glycaemic profile soon after patients are diagnosed with diabetes and mitigating long-term risk for diabetic complications and mortality. Best recent evidence on outcomes and management of PPDM – the *primus inter pares* in the DEP criteria – are overviewed in the companion article published in this issue of the Journal (115). Correct diagnosing and classifying of DEP will make it easier to counsel people on therapy options, improve individuals' satisfaction, and reduce burnout from frequent episodes of hypo- and hyperglycaemia. Further, appreciation of a complex (yet well-ordered) notion such as DEP by health insurance companies will make medical billing and reimbursement less intricate. It is also anticipated that this article will encourage pharmaceutical companies to help fill the apparent evidence gap and target studying people with PPDM, PCRD, and CFRD. The DEP criteria will

underpin the ability of future research to determine the optimal management for these patients and make routine clinical management of these individuals more tailored and evidence-based. Classification of diabetes continues to evolve (Table 3). Modifications of the DEP criteria will be required in the future, when new high-quality evidence is gathered. But, at this time, there is sufficient evidence and justification to apply the DEP criteria in both clinical practice and research.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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