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Diabetes of the exocrine pancreas: American Diabetes Association-compliant lexicon

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ABSTRACT

Multidisciplinary teams, including gastroenterologists, endocrinologists, surgeons, dietitians, primary care physicians, and other health professionals, are involved in management of individuals with diabetes of the exocrine pancreas (DEP). This necessitates introduction of a uniform terminology to ensure proper communication and reporting. Because DEP is a form of secondary diabetes mellitus, it makes sense to align the evolving DEP lexicon with nomenclature and diagnostic standards advocated by a world leading professional body in the field of diabetes such as the American Diabetes Association. This Editorial offers a historical excursus on the terms used and proposes a new concise nomenclature and diagnostic criteria. This new taxonomy of DEP, compliant with the American Diabetes Association standards of diagnosis and care for patients with diabetes mellitus, will ensure standardisation of reporting in future clinical studies on DEP and enable a dynamic incorporation of glucose dysregulation mechanisms related specifically to diseases of the exocrine pancreas as new evidence emerges.

Diabetes of the exocrine pancreas (DEP) has long been recognized as a distinct form of diabetes mellitus but research efforts were rather flaccid until the turn of the 20th century. The early 21st century witnessed the resurgence of interest in this area, predominantly driven by Dr Andersen [1–3] and Dr Chari [4–6] in the USA, Dr Ewald [7–9] in Germany, and COSMOS group in New Zealand [10–12]. This led to proliferation of researchers interested in expanding the evidential base for DEP and establishment of a major research collaboration called the 'consortium to study chronic pancreatitis, diabetes and pancreas cancer'. The other issue that hampered the progress in this area was the fact that the burden of diabetes in diseases of the exocrine pancreas has been largely unknown, at least in part because of the absence of robust epidemiological data at population level. This is in a stark contrast to type 1 and type 2 diabetes, where there are dozens of large population-based studies and, hence, the impact of those types of diabetes is duly appreciated.

However, the tide is turning as the first large population-based studies focused on non-selected individuals with diabetes associated with diseases of the exocrine pancreas have emerged in the past two years [13–15] and there is a reasonable hope that they have ushered in a new era of DEP research. The study by Shen et al. [13] included a total of 2966 individuals after acute pancreatitis and 11,864 matched controls from the general population (who had no prior diagnosis of diabetes or disease of the exocrine pancreas) and showed that, after adjustment for several covariates, the risk of new onset diabetes is 2.5 times higher among those who had an attack of acute pancreatitis. The study by Lee et al. [14] included a total of 3187 individuals after acute pancreatitis and 709,259 randomly selected controls from the general population and similarly showed that, after adjustment for several covariates, the risk of new onset diabetes is 2.1 times higher among those who had an attack of acute pancreatitis. This was followed by the study by Pendharkar et al. [15] that included a total of 110,042 individuals with diseases of the exocrine pancreas (acute pancreatitis, chronic pancreatitis, or pancreatic cancer) and showed that the prevalence of diabetes associated with them is 1.13 per 1000 general population (0.11%). This estimate is within the range of recently published estimates of type 1 diabetes prevalence in the general population and suggests that the frequency of DEP occurrence is at least no less than that of type 1 diabetes. Also, the study by Pendharkar et al. [15] formally confirmed what had been evident based on circumstantial evidence only [16,17] - that pancreatitis is the largest contributor to DEP.

To keep up with the advancing field of DEP, our lexicon should evolve to accommodate the emerging evidence and also to take into account the inter-disciplinary nature of management of this

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condition, involving gastroenterologists, surgeons, diabetologists, and other health professionals. Several terms are used in the literature to describe the presence of diabetes in patients with diseases of the exocrine pancreas. Historically, the first term was 'pancreatic diabetes' [18]. It was introduced in 1892, several decades before the discovery of insulin and delineation of the key metabolic pathways involving the islets of Langerhans, to denote the development of diabetes in animals after removal of the pancreas. It was followed by the term 'pancreatogenic diabetes' in the early 1970s [19] - the golden era of pancreaticoduodenectomy. The most recent term is 'type 3c diabetes', which was used from 2002 to 2014 in the classification of patients with diabetes issued by the American Diabetes Association (ADA) [20]. Although initially these terms were useful and allowed to put patients with diabetes in the setting of diseases of the exocrine pancreas into a separate category, currently this terminology is considered outdated and confusing in both clinical and research settings. The first two terms are rather anachronisms as nowadays it is established that, with very rare exceptions, development and progression of diabetes involves 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 [21–24]. Further, these terms seem to cloud the fact that a non-negligible fraction of patients has pre-existing unrecognised diabetes at the time of diagnosing their disease of the exocrine pancreas [25,26]. The term 'type 3 diabetes' was ultimately abandoned by the ADA [27], perhaps because it was a 'catch all' group that incorporated any type of diabetes other than type 1, type 2, and gestational diabetes. It might be tempting for some health professionals to use intuitive terms such as 'diabetes following pancreatic disease', 'diabetes secondary to pancreatic disease', or 'diabetes due to disease of the exocrine pancreas' to describe their population. However, these terms are suboptimal because they all connote causality. However, the reality is that, using the current standards of diagnosis and care, there is often no definitive prospective proof of the cause and effect relationship between a given disease of the exocrine pancreas and diabetes (e.g., pre-existing unrecognized diabetes first diagnosed during a hospitalization for acute pancreatitis or shortly after that, new onset diabetes in pre-symptomatic pancreatic ductal adenocarcinoma). The other important aspect is that the terminology currently used in the field of Gastroenterology/Surgery is misaligned linguistically with the terms used by the ADA to describe other forms of secondary diabetes, such as 'cystic fibrosis-related diabetes' and 'post-transplantation diabetes mellitus' [28].

It is time for the Gastroenterology/Surgery and Diabetology communities to rethink the terminology related to diabetes in the setting of diseases of the exocrine pancreas that we have gotten so used to, and redirect it in such a way that it is unified for all physicians, patients, and regulatory bodies involved with medical decisions and payment. This opinion article is considered the first step towards standardized nomenclature of DEP that will catalyse deliberation of major stakeholders, including ADA scientific leadership, and development of an international consensus. To promote understanding of diabetes pathophysiology, it is important to categorize DEP in terms of etiology and have specific terms for most common of them. The term 'cystic fibrosis-related diabetes' is already deeply ingrained in the lexicon of both diabetologists and gastroenterologists/surgeons and should remain there [20,28,29]. For the purpose of consistency, diabetes associated with pancreatic cancer is best to be termed 'pancreatic cancer-related diabetes'. Its important subgroup is new onset diabetes that predates the diagnosis of pancreatic ductal adenocarcinoma (Table 1), which appears to be a promising early marker of pancreatic cancer [4,6,30]. It is acknowledged that the diagnosis of new onset diabetes in pancreatic ductal adenocarcinoma (NOD-PDAC) is currently made retrospectively and development of specific diagnostic criteria for this entity is eagerly awaited. The use of several terms as a part of classification of diabetes should be discouraged. In particular, discomfort with the terms 'post-resection diabetes mellitus after pancreaticoduodenectomy', 'apancreatic diabetes', and suchlike arises from the fact that they artificially inflate the statistics related to DEP. This is because the underlying disease of the exocrine pancreas, which has been the indication for a major pancreatic surgery (most frequently, pancreatic cancer and chronic pancreatitis), is in itself frequently associated with diabetes. A term to cover this entity is best to be a part of classification of complications/sequelae after pancreatic surgery, not classification of DEP. Similarly, congenital dysfunctions of the pancreatic islets (e.g., pancreatic agenesis, hereditary hemochromatosis) are beyond the scope of DEP nomenclature.

Given that one out three patients with acute pancreatitis progresses to chronic pancreatitis (due to several shared elements of pathogenesis that link them together) and taking into account that the existence of a continuum from first attack of acute pancreatitis to chronic pancreatitis is well-established [31–35], it is sensible to formally designate no separate terms for diabetes resulting from each of them. It is acknowledged that patients at the extremes of the pancreatitis spectrum, i.e. diabetes after a single episode of acute pancreatitis and diabetes after a long-term definitive chronic pancreatitis, have different underlying pathophysiological mechanisms [1,3,36–43]. However, this may have implications for treatment (and, perhaps, prevention [44]) of diabetes in these patients but not for classifying them, as the ADA classification is etiology-based [20,27,28]. Two new terms are proposed (Fig. 1). 'New onset diabetes after pancreatitis' (NODAP) acknowledges the effect of acute or chronic pancreatitis on previously normal glucose homeostasis. NODAP excludes patients with diabetes, before and up to 3 months (as glycated hemoglobin reflects average plasma glucose over the previous 2–3 months) after hospital discharge with pancreatitis, which was previously unrecognized. The other term, 'post-pancreatitis diabetes mellitus' (PPDM), describes the presence of diabetes in the setting of acute or chronic pancreatitis

Table 1
American Diabetes Association-compliant nomenclature of diabetes of the exocrine pancreas.[a]

Post-pancreatitis diabetes mellitus (PPDM)[b]
• New onset diabetes after pancreatitis (NODAP)[c]
Pancreatic cancer-related diabetes
• New onset diabetes in pre-symptomatic pancreatic ductal adenocarcinoma (NOD-PDAC)
Cystic fibrosis-related diabetes

[a] Individuals with diseases of the exocrine pancreas and islet-specific autoantibodies to glutamic acid decarboxylase, insulinoma-associated protein 2, or zinc transporter antigen are deemed to have latent autoimmune diabetes of adults and should not be labelled as any form of diabetes of the exocrine pancreas.
[b] Elevated blood glucose during the course of acute pancreatitis and/or within 3 months after hospitalization in patients without previous diagnosis of diabetes is deemed stress hyperglycemia and should not be labelled as PPDM.
[c] Study reports should clearly indicate (under inclusion criteria) the type of pancreatitis patients studied (e.g., first episode of acute pancreatitis, chronic pancreatitis).

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