MANAGEMENT OF ENDOCRINE DISEASE

Post-pancreatitis diabetes mellitus: prime time for secondary disease

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Abstract

While most people with diabetes have type 2 disease, a non-negligible minority develops a secondary diabetes. Post-pancreatitis diabetes mellitus (PPDM) is an exemplar secondary diabetes that represents a sequela of pancreatitis – the most common disease of the exocrine pancreas. Although this type of diabetes has been known as a clinical entity since the late 19th century, early 21st century high-quality epidemiological, clinical, and translational studies from around the world have amassed a sizeable body of knowledge that have led to a renewed understanding of PPDM. People have at least two-fold higher lifetime risk of developing diabetes after an attack of pancreatitis than those in the general population without a history of diseases of the exocrine pancreas. PPDM is caused by acute pancreatitis (including non-necrotising pancreatitis, which constitutes the majority of acute pancreatitis) in four-fifth of cases and chronic pancreatitis in one-fifth of cases. Moreover, the frequency of incident diabetes is not considerably lower after acute pancreatitis than after chronic pancreatitis. Recurrent attacks of pancreatitis and exocrine pancreatic dysfunction portend high risk for PPDM, but are not mandatory for its development. Further, young- or middle-aged non-obese men have an increased risk of developing PPDM. In comparison with type 2 diabetes, PPDM is characterised by poorer glycaemic control, higher risk of developing cancer (in particular, pancreatic cancer), younger age at death, and a higher risk of mortality. Metformin monotherapy is recommended as the first-line therapy for PPDM. Appropriate screening of individuals after an attack of pancreatitis, correct identification of PPDM, and appropriate management is crucial with a view to improving the outcomes of this secondary but not inappreciable disease.

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Introduction

Diabetes has been around for millennia but its heterogeneity has become appreciated only over the past decennia. It is an umbrella term used for a group

of diseases defined by prolonged hyperglycaemia. Since the 1980s, age-standardised prevalence of diabetes in adults has increased (or at best remained unchanged)

Invited Author's profile

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in 200 countries (1). Together with population growth, this rise has led to a near quadrupling of the number of adults with diabetes worldwide. Several types of diabetes are recognised in modern classifications of diabetes emanating from major organisations, and type 2 is clearly the diabetes behemoth. However, type 2 diabetes mellitus (T2DM) in itself is a disease of exclusion, which means that it exists only when other diseases (such as type 1 diabetes and what is labelled in both the 2019 World Health Organisation classification and the 2020 American Diabetes Association classification ‘other specific types of diabetes’) are absent (2, 3). If one uses the analogy of arterial hypertension, while essential (idiopathic) hypertension is the most common type, 5–10% of people with arterial hypertension are affected by a specific cause of increased blood pressure levels called ‘secondary hypertension’. This includes several diseases that are observed in endocrinology practice such as primary aldosteronism, pheochromocytoma, thyroid disease, and Cushing syndrome. It has been conclusively shown that, if appropriately diagnosed, people with ‘secondary hypertension’ could be properly treated, achieving optimal control of blood pressure levels with a lower number of antihypertensives and a significant reduction of cardiovascular risk (4).

In the field of diabetology, it is argued that the 21st century discoveries that got translated into improved treatments and outcomes of people with diabetes have mostly come from the ‘other specific types of diabetes’ category (hereafter referred to as ‘secondary diabetes’). For example, the discovery that a large fraction of people with neonatal diabetes (a type of secondary diabetes) have heterozygous mutations affecting the *Kir6.2* subunit of the ATP-sensitive potassium channel in the pancreatic β -cells led to the transition from insulin to sulfonylurea therapy, which not only made these people insulin-free but also improved glycaemic control (5). Similarly, the detailed characterisation of another type of secondary diabetes – maturity-onset diabetes of the young – enabled the switch of people (with hepatocyte nuclear factor-1 α mutations) previously on insulin to sulfonylureas (6). This review puts diabetes secondary to pancreatitis – one of the most common digestive diseases (7) – in the spotlight. It provides the most up-to-date information on the epidemiology, risk factors, pathogenesis as well as the best available evidence on clinical outcomes and treatment. Practical aspects of diagnosing and classifying are discussed in the companion article published in this issue of the Journal (8).

Epidemiology

Post-pancreatitis diabetes mellitus (PPDM) is a core feature of diabetes of the exocrine pancreas (DEP) (9, 10). As there are two main types of pancreatitis (acute pancreatitis (AP) and chronic pancreatitis (CP)), two subtypes of PPDM – post-acute pancreatitis diabetes mellitus (PPDM-A) and post-chronic pancreatitis diabetes mellitus (PPDM-C) – are recognised in people without pre-existing diabetes (11). Because diabetes may remain undiagnosed prior to or during hospitalisation for pancreatitis, the term ‘new-onset diabetes after pancreatitis’ (NODAP) is adopted to describe individuals with PPDM who had documented normal glucose homeostasis at baseline (as evidenced by conclusive HbA_{1c} and/or fasting plasma glucose (FPG) values). A nationwide population-based study by the COSMOS group found that the incidence of DEP in New Zealand was 2.8 and per 100 000 general population in 2010 (12). In particular, the incidence of PPDM-A and PPDM-C was 1.8 per 100 000 general population per year and 0.5 per 100 000 general population per year, correspondingly. A similar estimate of the incidence of DEP was reported in a population-based study from the UK – 2.6 per 100 000 general population per year (9). The study also found that DEP is the second most common type of new-onset diabetes in adults (1.8% for DEP as compared with 1.1% for type 1 diabetes) (9).

Three nationwide population-based studies (two from Taiwan and one from Israel) compared the risks of developing diabetes in individuals after the first attack of AP vs those from general population (13, 14, 15). The study by Lee *et al.* (13) included 3187 adults (with no prior diabetes) who survived the first attack of AP and 709 259 randomly selected controls from the general population (with no prior diabetes or AP). It found that the adjusted risk of newly diagnosed diabetes was 2.15 (95% CI: 1.92–2.41) times higher among those who had an attack of AP. The study by Shen *et al.* (14) included 2966 adults (with no prior diabetes) who survived the first attack of AP and 11 864 controls from the general population (with no prior diabetes or disease of the exocrine pancreas), individually matched for age and sex with a ratio of 1:4 without replacement. It found that the adjusted risk of newly diagnosed diabetes was 2.54 (95% CI: 2.13–3.04) times higher among those who had an attack of AP. The study by Bendor *et al.* (15) included 281 adolescents (with no prior diabetes) who survived first attack of AP and 1 801 716 adolescents from the general population (with no prior diabetes or disease of the exocrine pancreas).

It found that the most adjusted risk of newly diagnosed diabetes in adulthood was 2.10 (95% CI: 1.15–3.84) times higher among those who had a single attack of AP.

Another nationwide population-based study by the COSMOS group investigated the prevalence of DEP (16). The crude prevalence of DEP was 1.13 (95% CI: 1.12–1.14) per 1000 general population. AP was the underlying cause in the majority (61%) of DEP cases. The crude prevalence of PPDM-A was 77 (95% CI: 77–78) and PPDM-C – 10 (95% CI: 9–11) per 1000 individuals with diseases of the exocrine pancreas. These data are not surprising as AP is the most common disease of the exocrine pancreas (the incidence of 34 per 100 000 general population per year) worldwide – far more common than CP (the incidence of 9 per 100 000 general population per year) (7).

The frequency of newly diagnosed diabetes after AP or CP was investigated in dozens of clinical studies and pooled together in two meta-analyses (Table 1). A 2014 meta-analysis by the COSMOS group statistically aggregated follow-up data from 24 clinical studies of individuals after the first attack of AP (17). The study had robust eligibility criteria, with all individuals who were diagnosed with diabetes or prediabetes prior to AP, diagnosed with CP, underwent pancreatic resection being excluded. The study found that 23% (95% CI: 16–31%) of people after the first attack of AP developed PPDM-A. The methodology was emulated in 2019 by a group from China that statistically aggregated follow-up data from 15 clinical studies of individuals with CP (including those who progressed from AP to CP) (18). The study found that 30% (95% CI: 27–33%) of people developed PPDM-C. This suggests that the up to 86% estimates of frequency of diabetes mellitus in CP in earlier studies were inflated (19, 20), at least in part because of the inclusion of individuals with pre-existing diabetes. Given that the later meta-analysis (18) included studies with both prospective

and retrospective follow-ups (whereas the former was constrained to prospective follow-up only (17)) and taking into account that at least 8% of individuals after the first attack of AP progress to CP (21), it appears that the frequency of newly diagnosed diabetes after AP vs CP is not materially different.

Both meta-analyses attempted to analyse the PPDM trend with time (17, 18) but the findings were inconclusive as none of the primary studies investigated glycaemia at multiple time points and standardised intervals during follow-up. The 2020 LACERTA study by the COSMOS group (22) was the first prospective longitudinal cohort study of changes in glycaemia at regular structured time points in unselected AP patients (i.e. regardless of aetiology, severity, and recurrence of AP at baseline). It enrolled patients without diabetes (both diagnosed and undiagnosed, the latter was defined as HbA1c $\geq$ 48 mmol/mol (6.5%)) at the time of hospitalisation for AP and followed up their temporal changes in HbA1c and FPG every 6 months over 24 months. All participants were followed-up in-person (i.e. 'remote' follow-ups were deemed unacceptable). The cumulative incidence of NODAP (defined in line with the American Diabetes Association guidelines) was 3.3% at 6 months, 7.2% at 12 months, 9.2% at 18 months, and 11.2% at 24 months follow-up ($P=0.008$) (Fig. 1). The LACERTA study provided the strongest to date evidence to justify regular follow-ups of high-risk individuals after an attack of AP.

Risk factors

Sex differences

Men and women generally have a similar risk of T2DM. By contrast, men are at a considerably heightened

Table 1 Characteristics of the pooled analyses of post-acute pancreatitis diabetes mellitus and post-chronic pancreatitis diabetes mellitus. Data on post-acute pancreatitis diabetes mellitus are derived from Das *et al.* (17). Data on post-chronic pancreatitis diabetes mellitus are derived from Zhu *et al.* (18).

Characteristics	Post-pancreatitis diabetes mellitus	
	Post-acute	Post-chronic
Studies included, <i>n</i>	24	15
Patients with pancreatitis, <i>n</i>	1102	8970
Patients with pre-existing diagnosis of diabetes excluded	Yes	Yes
Patients who underwent pancreatic surgery excluded	Yes	No
No. of studies with prospective follow-up of glucose homeostasis	24/24	13/15
Frequency of diabetes overall, % (95% CI)	23% (16–31)	30% (27–33)
95% CI	16–31%	27–33%
Frequency of diabetes treated with insulin, % (95% CI)	15% (9–21)	17% (13–22)
95% CI	9–21%	13–22%

Figure 1

Incidence of new-onset diabetes within two years of an attack of acute pancreatitis. Diabetes was defined based on the American Diabetes Association guidelines. Data are derived from Bharmal *et al.* (22).

risk for PPDM than women. A population-based study from Taiwan showed that both men and women had significantly higher risks for PPDM-A than people in the general population (14). However, the risks were significantly higher in men (adjusted hazard ratio (HR): 3.21; 95% CI: 2.59–3.98) than in women (adjusted HR: 1.58; 95% CI: 1.14–2.20) ($P=0.0004$). A population-based study by the COSMOS group showed that men had a significantly higher prevalence of DEP at 1.32 (95% CI: 1.31–1.33) per 1000 general population compared with women at 0.93 (95% CI: 0.92–0.94) per 1000 general population ($P < 0.05$) (16). Notably, this difference was attributed to PPDM alone as the prevalence of pancreatic cancer-related diabetes did not differ significantly between the sexes. Specifically, the prevalence of PPDM-A was significantly ($P < 0.05$) different between men and women at 93.28 (95% CI: 92.78–93.78) per 1000 patients with diseases of the exocrine pancreas and 62.13 (95% CI: 61.70–62.56) per 1000 patients with diseases of the exocrine pancreas, respectively (16). Similarly, the prevalence of PPDM-C was significantly ($P < 0.05$) different between men and women at 14.17 (95% CI: 13.97–14.37) per 1000 patients with diseases of the exocrine pancreas and 6.24 (95% CI: 6.10–6.38) per 1000 patients with diseases of the exocrine pancreas, respectively. Subsequent population-based studies from other settings invariably demonstrated a markedly higher proportion of men than women among people with PPDM (9, 15).

Age

It is well recognised that middle-aged and older adults have the highest risk for T2DM. By contrast, the weight of evidence indicates that the age-specific risk for PPDM is the highest among young- and middle-aged adults. A nationwide population-based study from Israel followed up individuals aged 16–20 and showed that the mean time to newly diagnosed diabetes was 4.5 years shorter in individuals with a history of a single attack of AP in comparison with those from the general population (who had no prior disease of the exocrine pancreas) (15). The study also investigated various cut-offs of age at the time of diagnosis of diabetes and found that individuals under the age of 40 with a history of AP had the highest risk of developing diabetes (adjusted odds ratio (OR): 4.65; 95% CI: 2.48–8.72) in comparison with the general population. A population-based study of adults with newly diagnosed diabetes (age 18 years or older) from the UK showed that individuals aged 30–39 (OR: 1.68; 95% CI: 1.20–2.35) and 20–29 (OR: 4.25; 95% CI: 2.58–7.01) with a history of disease of the exocrine pancreas had significantly higher risks of newly diagnosed diabetes than those in the general population (who had no prior disease of the exocrine pancreas) (9). Individuals aged 40–59 had equal risks of DEP and T2DM whereas those aged 60–79 tended to have a higher risk for T2DM than DEP (9). A population-based study of adults (age 18 years or older) from Taiwan showed that, while the incidence of newly diagnosed diabetes expectedly increased with age in both sexes of the general population, the incidence of PPDM-A increased with age only in women (but not in men) with a history of AP (14). In fact, the highest age-specific risk of newly diagnosed diabetes was observed in men under the age of 45 (adjusted HR: 7.46; 95% CI: 5.12–10.87) followed by men aged 45–64 (adjusted HR: 2.61; 95% CI: 1.79–3.83). The interaction between age and history of AP was statistically significant for men ($P < 0.0001$), but not for women. The findings did not change materially when the analysis was constrained to individuals with mild AP only or single attack of AP only (14).

Body composition

Obesity or overweight (as determined by BMI) is a key risk factor for T2DM. By contrast, the risk for PPDM increases in lean or overweight individuals. A general population-based study from Israel showed that, while individuals with a history of AP overall were at 2.10 (95%

CI: 1.15–3.84) times higher risk for newly diagnosed diabetes, the risk was accentuated when the analysis was constrained to individuals with normal BMI (adjusted OR: 3.09; 95% CI: 1.57–6.08) (15). It is important to note that the norm was defined as BMI in the 5–84 percentile range. A general population-based study from the UK used the conventional BMI ranges and demonstrated that, while the proportion of overweight individuals did not significantly differ between adults with PPDM-A vs T2DM, a significantly lower proportion of individuals with PPDM-A were obese (OR: 0.77; 95% CI: 0.63–0.95) and a significantly higher proportion of individuals with PPDM-A were lean (OR: 1.59; 95% CI: 1.14–2.22) (9).

A series of MRI studies by the COSMOS group investigated the role of adipose tissue distribution in individuals after pancreatitis (who had a median BMI of 28 kg/m²) (23, 24, 25, 26, 27). Visceral fat volume and intra-pancreatic fat deposition (but not subcutaneous fat volume or liver fat deposition) were significantly increased in individuals after AP who developed diabetes (28, 29). Interestingly, while visceral fat volume explained 22% of variance in intra-pancreatic fat deposition in the overall cohort of individuals after AP, the stratified analysis according to the diabetes status revealed that visceral fat volume explained 44% of variance in intra-pancreatic fat deposition in individuals without diabetes and only 14% of variance in intra-pancreatic fat deposition in individuals with diabetes (29). This suggests that intra-pancreatic fat deposition may be a risk factor for PPDM independently of visceral fat. In fact, a comprehensive analysis of body composition and insulin traits showed that the Raynaud index (a fasting index of insulin sensitivity) was the best biomarker of intra-pancreatic fat deposition (explaining 20% of its variance) in individuals with NODAP (28). Moreover, intra-pancreatic fat deposition was significantly inversely associated with insulin sensitivity in individuals with NODAP only, but not in those with T2DM or healthy controls (30).

Recurrent attacks of pancreatitis

A population-based study from Taiwan included 12 284 individuals after the first attack of AP and found that those with two or more recurrences of AP had a significantly increased risk of PPDM (OR: 1.94; 95% CI: 1.48–2.40; $P < 0.001$) (31). A complementary population-based study by the COSMOS group included a total of 2147 individuals after the first attack of AP who underwent cholecystectomy and investigated the effect of recurrent biliary events (a composite endpoint that

includes recurrent AP) prior to cholecystectomy on the risk of PPDM. The study found that, while one recurrence was not significantly associated with the risk of PPDM (adjusted HR: 0.93; 95% CI: 0.56–1.52), two recurrences (adjusted HR: 1.97; 95% CI: 1.04–3.76) and three or more recurrences (adjusted HR: 2.77; 95% CI: 1.34–5.72) were associated with significantly increased risks of PPDM. The findings of the two population-based studies above (31, 32) are aligned well with the results of a MRI study by the COSMOS group on pancreas volumetry in individuals after AP (without signs of CP) as compared with healthy controls (33). A significant 22% reduction in total pancreas volume was demonstrated in individuals after two or more recurrences of AP, but not in those with one or no recurrence. Further, pancreas tail (which is known to have the highest proportion of the islet of Langerhans), but not head or body, was significantly reduced in individuals after two or more recurrences of AP (33). The above findings were independent of age, sex, HbA1c, and BMI – all of which are known to affect pancreas volume (34, 35). A study from Germany showed a similar reduction in total pancreas volume (by 21%) in individuals with histology-verified CP as compared with controls (36). Further, the reduction in total pancreas volume was directly proportional to the reduction in β -cell mass (36).

Exocrine pancreatic dysfunction

There is abundant evidence that individuals with diabetes mellitus have a high frequency of exocrine pancreatic dysfunction. For example, total pancreas volume (as a proxy for secretory reserve of pancreatic acinar cells) was investigated in 55 studies in people with diabetes (34) and direct or indirect exocrine pancreatic function tests were studied in 26 studies in people with diabetes (37). By contrast, until very recently, there has been a paucity of strong evidence on the converse relationship (i.e. exocrine pancreatic dysfunction as a risk factor for new-onset diabetes) (38, 39). The only well-recognised example was cystic fibrosis, in which mutations in the *CTFR* gene result in exocrine pancreatic dysfunction that leads to cystic fibrosis-related diabetes (a subtype of DEP). A 2019 whole-exome sequence analysis from the USA discovered that mutations in another gene, *CELA2*, result in low circulating levels of the pancreatic elastase that it encodes and lead to hyperglycaemia, decreased insulin secretion, and increased insulin clearance (40). Low circulating levels of other pancreatic enzymes (amylase, lipase) were found to be significantly associated with hyperglycaemia in a 2020 systematic review and meta-analysis by the

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COSMOS group (41). A 2020 population-based study by the COSMOS group investigated individuals after either AP or CP without a history of both exocrine pancreatic dysfunction and diabetes mellitus at baseline (42). The analysis was constrained to individuals with more than 1 year between exocrine pancreatic dysfunction and PPDM, exocrine pancreatic dysfunction was considered as a time-varying risk factor, and multivariable Cox regression analysis was conducted to adjust for possible confounders. The study showed that exocrine pancreatic dysfunction was associated with a significantly higher risk of PPDM (adjusted HR: 2.51; 95% CI: 1.38–4.58). Notably, the estimate further increased in individuals with mild AP (adjusted HR: 4.65; 95% CI: 2.18–9.93), indicating that the severity of AP did not affect the studied association (42). Other characteristics of pancreatitis (e.g. aetiology) also did not materially affect the association between exocrine pancreatic dysfunction and the risk of developing PPDM. Further, individuals with CP and exocrine pancreatic dysfunction (adjusted HR: 3.14; 95% CI: 1.44–6.84) were at a no higher risk for PPDM than individuals with AP and exocrine pancreatic dysfunction (adjusted HR: 4.85; 95% CI: 2.57–9.16). The previous findings set the stage for carefully designed prospective studies on the use of pancreatic enzyme supplementation after hospital discharge of individuals with pancreatitis with a view to reducing the risk for PPDM. More broadly, a paradigm shift is looming as the exocrine pancreas appears to be actively involved in more than digestion (43).

Other pancreatitis-related factors

The prevailing dogma in the past was that PPDM-A develops only in people with severe AP. It was challenged in 2014 when a comprehensive meta-analysis and meta-regression by the COSMOS group was published (17). The study showed that individuals with mild AP (who constitute the majority of AP cases) were at a high risk of developing PPDM and the severity of AP did not materially affect the risk of developing PPDM. The next line of evidence came from population-based studies published in 2015–2016 (13, 14). The study by Lee *et al.* (13) found that the adjusted risk of PPDM in the overall AP cohort was 2.10 (95% CI: 1.92–2.41) and it did not change materially when the analysis was constrained to individuals with severe AP only (adjusted HR: 2.22; 95% CI: 1.50–3.29). The study by Shen *et al.* (14) showed that the adjusted risk of PPDM in the overall AP cohort was 2.54 (95% CI: 2.13–3.04) and it did not change materially when the analysis was constrained to individuals with mild AP only (adjusted HR: 2.49; 95% CI: 2.04–3.04). Taken together, the above studies have established that

people with a history of AP are at high risk for developing PPDM irrespective of the severity of attack.

The association between aetiology of AP and risk of PPDM was found to be statistically significant in only one population-based study. The study by Ho *et al.* (31) showed that alcohol-related AP, determined based on hospital discharge codes, was associated with a significantly increased risk of PPDM (OR: 1.89; 95% CI: 1.52–2.27) in comparison with biliary AP. However, this could be ascribed not to the inherently different risks of PPDM in regards to aetiology but to the fact that individuals with biliary AP often undergo cholecystectomy. Cholecystectomy in individuals with biliary AP prevents recurrent biliary events (and, therefore, reduces the risk of PPDM) whereas there is no effective and widely adopted treatment strategy to prevent recurrence in individuals with alcohol-related AP (32, 44). The 2014 meta-analysis and meta-regression of 24 clinical studies (that tend to be more accurate in ascertaining aetiology of AP than population-based studies) mentioned above found no evidence to suggest a differential effect of alcohol-related or biliary aetiology of AP on the risk of PPDM (17).

Pathogenesis

Throughout most of the 20th century, AP and CP were considered two distinct entities. Further, it was believed that *restitutio ad integrum* occurs in AP – a complete healing of the pancreas after an attack of pancreatitis. It was only in the 1990s that it was the first theorised that pancreatitis may represent a disease continuum (45). Fast forward two decades, a 2015 systematic review and meta-analysis of observational studies with at least 1 year of follow-up by the COSMOS group (21) showed that 22% of individuals after their first attack of AP developed recurrent attacks and 36% of individuals after recurrent AP developed CP, therefore demonstrating conclusively that pancreatitis often lies on a continuum (Fig. 2). Correspondingly, there is a gradual change in the pathogenesis of PPDM along this continuum: from increased insulin resistance after the first attack of (non-necrotising) AP to a permanent loss of β -cell function in end-stage CP (11, 46). Although PPDM-A and PPDM-C are conceptually viewed as mutually exclusive entities, it may not be easy to distinguish diabetes following recurrent AP vs early CP. The companion article in this issue provides a guidance on the differential diagnosis (8). What is most important for the practicing diabetologist though is to appreciate diabetes at polar ends of the PPDM spectrum – that is diabetes following the first attack of (non-

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Figure 2

Key pathophysiological changes along the post-pancreatitis diabetes mellitus continuum. AP, acute pancreatitis; CP, chronic pancreatitis; PPDM-A, post-acute pancreatitis diabetes mellitus; PPDM-C, post-chronic pancreatitis diabetes mellitus.

necrotising) AP and diabetes following end-stage CP. This is because the key pathogenetic drivers – heightened insulin resistance and irreversible β -cell failure, correspondingly – will dictate the need for differing treatments. At the same time, distinguishing the subtypes of diabetes in the middle of the PPDM spectrum (e.g. diabetes following recurrent AP or diabetes following early stage of CP) may be less important for the practicing diabetologist. The two subtypes of PPDM represent a compromise with a view to standardising the terminology and the limitation of creating categorical states from continuously distributed phenomena must be kept in mind.

The DORADO (47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58) and MENSA (59, 60, 61) projects by the COSMOS group brought us closer to a comprehensive narrative of the mediators that drive PPDM following non-necrotising AP. The two projects characterised more than 50 analytes (both fasting and mixed meal test-stimulated) in abnormal glucose tolerance after AP as compared with normal glucose tolerance. Results of these projects are summarised in Table 2 and show that PPDM-A is characterised by broad pathological signatures in chronic low-grade inflammation, lipid metabolism, iron metabolism, and dysfunction of the pancreas-gut-brain axis. The studied mediators and the key known pathways in the pathogenesis of PPDM were reviewed in detail elsewhere (46). One mediator that is worth highlighting is oxyntomodulin as a significant decrease in its fasting and postprandial levels was demonstrated in individuals with NODAP in comparison with matched individuals with T2DM and healthy controls (61). This gut peptide is a rather enigmatic derivative of proglucagon but, unlike its ‘cousin’ glucagon-like peptide-1, oxyntomodulin is involved in the regulation of exocrine pancreatic function. This is achieved through cholecystokinin (a well-known pancreatic secretagogue) (49) and a vagal neural indirect mechanism (62, 63). Oxyntomodulin holds promise as a biomarker to distinguish PPDM from T2DM.

Glycaemic control

PPDM is more difficult to control than T2DM. A large primary care study from the UK showed that mean ($\pm$ S.D.) HbA1c levels at the time of diabetes diagnosis were significantly higher in individuals with DEP than

Table 2 Blood-based signatures of post-acute pancreatitis prediabetes or diabetes. The comparator was euglycaemia after acute pancreatitis or health.

Mediator	Fasted state	Reference	Postprandial state	Reference
Insulin	Increased	(47, 51)	Increased	(59)
C-peptide	No difference	(47)	Increased	(59)
Pancreatic polypeptide	Decreased	(47)	No difference	(59)
Amylin	Increased	(51)	No difference	(59)
Calcitonin gene-related peptide	Decreased	(53)	Not studied	
Interleukin-6	Increased	(48)	Not studied	
Glucose-dependent insulintropic polypeptide	No difference	(55)	Increased	(60)
Oxyntomodulin	Decreased	(49)	Decreased	(60, 61)
Glicentin	Decreased	(49)	Not studied	
Vasoactive intestinal peptide	Decreased	(49)	Not studied	
Gastrin-releasing peptide	Increased	(52)	Not studied	
Hepcidin	Increased	(58)	Not studied	
Ferritin	Decreased	(58)	Not studied	
Triglycerides	Increased	(50, 54)	Not studied	
Glycerol	Increased	(50, 54)	Not studied	

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those with T2DM: 67 (± 26) mmol/mol (8.3 (± 2.4)%) vs 63 (± 22) mmol/mol (7.9 (± 2.0)%); $P = 0.002$ (9). The difference remained statistically significant at 1 year (54 (± 16) mmol/mol (7.1 (± 1.5)%) vs 51 (± 13) mmol/mol (6.8 (± 1.2)%); $P < 0.001$) and 5 years (60 (± 18) mmol/mol (7.6 (± 1.7)%) vs 55 (± 15) mmol/mol (7.2 (± 1.4)%); $P < 0.001$) after diabetes diagnosis. The associations did not change materially when the analysis was constrained to individuals with PPDM-A only. Poor glycaemic control (defined as HbA1c > 53 mmol/mol (7%)) was observed in 40% of DEP cases at 1 year and 62% of DEP cases at 5 years after diabetes diagnosis (9). This translated into significantly higher likelihoods of poor glycaemic control in DEP vs T2DM at 1 year (adjusted OR: 1.3 (95% CI: 1.1–1.6)) and 5 years (adjusted OR: 1.7 (95% CI: 1.3–2.2)) after diabetes diagnosis. The proportion of individuals who had poor glycaemic control was very similar between PPDM-A and PPDM-C at 1 year after diabetes diagnosis (39 and 43%, respectively) and 5 years after diabetes diagnosis (62 and 65%, respectively). The analyses were adjusted for several important covariates including (but not limited to) age, sex, and BMI (9).

A clinical study from India compared glucose variability in individuals with PPDM-C ($n = 55$) vs T2DM ($n = 56$) using continuous glucose monitoring for 3–5 days (64). The groups were comparable in terms of HbA1c levels, FPG levels, postprandial glucose levels, duration of diabetes, proportion of individuals treated with insulin, calorie intake, and sex distribution. However, individuals with PPDM-C were significantly younger at the time of diabetes diagnosis and had lower BMI. None of the individuals underwent pancreatic resection. The study found that five out of the six indices of glucose variability were significantly increased in individuals with PPDM-C (64). Interestingly, one of the studied indices (mean amplitude of glucose excursion) had a significant inverse association with BMI in individuals with PPDM-C, but not those with T2DM. Further, BMI (together with HbA1c levels) explained 90% of the variance in mean amplitude of glucose excursion in PPDM-C whereas BMI was not associated with any index of glucose variability in T2DM.

Long-term outcomes

A series of nationwide studies conducted by the COSMOS group shed the first light on long-term outcomes (observation period up to 18 years) of individuals with PPDM. The risk of cardiovascular disease requiring hospitalisation was not significantly different between

individuals with PPDM and T2DM (65). However, the risks of renal disease and infectious disease requiring hospitalisation were significantly increased by 33 and 32%, respectively, in individuals with PPDM vs T2DM (65). In the subgroup analysis, the risks were significantly higher in both PPDM-A and PPDM-C as compared with T2DM. Individuals with PPDM also had a significantly higher risk of chronic pulmonary disease requiring hospitalisation, though this was observed in individuals with PPDM-C only (65). PPDM was significantly associated with a 88% higher risk of gout in a cohort of individuals with pancreatitis and no pre-existing gout; however, the analysis stratified by sex revealed that this association remained statistically significant in women only (66). Besides, individuals with PPDM were at a 4.4 times significantly higher risk of developing mental disorders in a cohort of individuals with pancreatitis and no pre-existing diabetes (67). This association was much stronger in PPDM-A (adjusted HR: 7.10; 95% CI: 4.14–12.19) than PPDM-C (adjusted HR: 2.97; 95% CI: 1.83–4.82).

Individuals with PPDM had the rate of all-cause mortality at 80.5 per 1000 person-years whereas those with T2DM had it at 65.6 per 1000 person-years (Fig. 3). This translated into 14.8 excess deaths per 1000 person-years and a 13% higher adjusted risk of all-cause mortality compared with individuals with T2DM (65). Also, individuals with PPDM had a significantly younger mean age at death than those with T2DM (67.8 vs 70.0 years, $P < 0.001$) (65). When cause-specific mortality was analysed, cardiovascular mortality was the most common cause of death in PPDM (mortality rate: 25.2 per 1000 person-years) and the mortality rate was very similar to that of T2DM (68). The second most common cause of death in PPDM was cancer (mortality rate: 22.8 per 1000 person-years). The cancer mortality rate was 44% significantly higher in PPDM vs T2DM and accounted for 9.4 excess deaths per 1000 person-years. Gastrointestinal disease and infectious disease mortality accounted for 5.5 and 5.0 excess deaths per 1000 person-years, respectively. These mortality rates were markedly lower than the one of cancer, yet they were significantly higher in PPDM vs T2DM (65).

It is important to note that the differences in cancer (and all-cause) mortality between PPDM and T2DM presented above were conservative as individuals with pancreatic cancer during the entire study period were intentionally excluded. A separate study compared the risk of developing primary pancreatic cancer in PPDM vs T2DM and showed that PPDM conferred a seven times significantly higher risk for pancreatic cancer (adjusted

Figure 3

Cause-specific mortality rates in post-pancreatitis diabetes mellitus versus type 2 diabetes mellitus. Data are derived from Cho *et al.* (65). T2DM, type 2 diabetes mellitus; PPDM, post-pancreatitis diabetes mellitus.

HR: 6.94; 95% CI: 4.09–11.77) (68). In order to examine the possible impact of reverse causality between diabetes and pancreatic cancer, a 12-month lag period between diabetes diagnosis and pancreatic cancer diagnosis was introduced and the results did not change materially (adjusted HR: 7.93; 95% CI: 3.53–17.81). Moreover, the study investigated the temporal relationship between diabetes and pancreatitis and found that diabetes that develops after pancreatitis (i.e. PPDM) was a much stronger risk factor for primary pancreatic cancer than T2DM that precedes pancreatitis (68). Specifically, individuals with PPDM had a 2.3 times significantly higher risk of pancreatic cancer (95% CI: 1.12–4.93), even after adjustment for covariates (68). This suggests that the increased risk of pancreatic cancer in individuals with PPDM is not due to merely the effect of pancreatitis as a comorbidity in individuals with T2DM but rather pancreatitis exerts an effect beyond being a comorbidity in individuals with PPDM. How exactly an attack of pancreatitis in individuals with diabetes has a differential effect on the subsequent risk of pancreatic cancer depending on whether it occurs before or after diabetes needs to be elucidated in future studies (69, 70).

Antidiabetic medications

There is a lack of studies on the effect of antidiabetic medications on short-term outcomes (e.g. glucose control) in PPDM. Findings from most seminal prospective studies

in the field of diabetes (e.g. UK Prospective Diabetes Study, the Diabetes Control and Complications Trial) cannot be legitimately extrapolated to individuals with PPDM as those studies typically excluded participants with a history of pancreatitis. Circumstantial evidence came from a 2017 study of individuals with newly diagnosed diabetes from the UK that investigated the rates of insulin use in 559 individuals with DEP (including 361 with PPDM-A) as compared with T2DM (9). It found that the rate of insulin use at 1 year after diabetes diagnosis was 9.6 times higher in DEP altogether and 6.4 times higher in PPDM-A specifically. At 5 years after diabetes diagnosis, the rate of insulin use was 7.4 times higher in DEP and 5.2 times higher in PPDM-A. The above analyses were adjusted for several important covariates including (but not limited to) age, sex, and BMI (9). Taken together with the findings from the same study on significantly worse glycaemic control at both 1 and 5 years after diabetes diagnosis in PPDM vs T2DM (presented above), it appears that a much earlier commencement of insulin therapy in PPDM (including, most notably, PPDM-A) did not lead to better glycaemic control.

The effect of antidiabetic medications on long-term outcomes in PPDM was investigated in a 2019 pharmacoepidemiological study by the COSMOS group (71). The linkage of nationwide pharmaceutical data (prescribed by primary, secondary, or tertiary healthcare providers) and hospitalisation data from all the District Health Boards in the country enabled the group to virtually rule out selection bias. The study included 836 individuals with PPDM (including 620 with PPDM-A) and investigated the associations between metformin use, insulin use, and mortality (never use of antidiabetic medications was set as the reference). Individuals with PPDM who never used antidiabetic medications had 68 excess deaths per 1000 person-years compared with individuals with T2DM who never used antidiabetic medications. In the analysis constrained to the first prescribed antidiabetic medication, metformin monotherapy was associated with a significantly lower risk of mortality (adjusted HR: 0.22; 95% CI: 0.09–0.53) (71). The median first prescribed metformin dose was 1000 mg/day. In the analysis constrained to long-term use of antidiabetic medications, ever use of metformin was associated with a significantly lower mortality (adjusted HR: 0.50; 95% CI: 0.36–0.70). The risk reduction was more pronounced in PPDM-A than PPDM-C (51% vs 37%), though not significantly different. Further, the beneficial effect of metformin use was compared between PPDM and T2DM and the lower mortality risk associated with metformin use was found

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to be 25% more pronounced in individuals with PPDM (adjusted HR: 0.75; 95% CI: 0.72–0.77) (71). Given that individuals with PPDM tend to be at an increased risk of hospitalisation for chronic kidney disease than those with T2DM (68), one could argue that the use of metformin in PPDM may put them at high risk of lactic acidosis. However, a 2010 Cochrane systematic review found that metformin treatment did not increase the incidence of lactic acidosis compared with other antidiabetic drugs in T2DM (72). Further, several more recent large cohort studies consistently showed a non-inferiority (or superiority) of metformin even in T2DM individuals with an estimated glomerular filtration rate between 30 and 45 mL/min/1.73 m² (i.e. category G3b) (73, 74, 75).

Insulin therapy (alone or in combination with other antidiabetic medications) as the first-line therapy in PPDM was not associated with a significantly lower risk of mortality (adjusted HR: 0.86; 95% CI: 0.40–1.84) (71). Long-term use of insulin also did not offer a significant survival benefit (adjusted HR: 0.71; 95% CI: 0.44–1.12). Moreover, long-term use of insulin in insulin-naïve individuals with the first attack of AP was associated with a significantly higher risk of progression to recurrent AP or CP (adjusted HR: 1.56; 95% CI: 1.15–2.11) in comparison with never-users of insulin (76). This held true irrespective of the time of diabetes onset, severity of AP, aetiology of AP, as well as the lag periods between the first attack of AP and the first use of insulin. Moreover, there was a significant dose-response relationship between insulin dose and the risk of progression of pancreatitis among insulin users (76). This COSMOS study on the association between the use of insulin and risk of progression of pancreatitis complemented several earlier population-based studies (77, 78) that showed that the use of insulin was associated with a significantly higher risk for pancreatic cancer – for which pancreatitis is one of the strongest risk factors (79). The above novel findings, coupled with the well-known adverse effects of insulin (such as hypoglycaemia and increased fat accumulation), justify a more cautious use of insulin in individuals with a history of AP. Only when the short-term benefits of lowering blood glucose levels with the use of insulin are expected to outweigh the long-term risks associated with progression of pancreatitis, the administration of insulin can be justified. A 2018 randomised controlled trial in individuals with cystic fibrosis-related diabetes (a subtype of DEP that is characterised by insulin deficiency) showed that an oral glucose-lowering drug (repaglinide) is non-inferior to insulin in controlling blood glucose (80). A wide

array of oral glucose lowering drugs is currently available, which warrants purposely designed randomised controlled trials with a view to determining the optimal treatment strategy to control blood glucose in PPDM.

Conclusions

Most people given a diagnosis of diabetes are naturally seeking clarity about the underlying cause that led them to become diseased in the first place. While providing a meaningful and unambiguous answer to those with T2DM is a challenge, the answer is quite straightforward to the uninitiated with secondary diabetes such as PPDM. Since the endocrine and exocrine pancreas reside in the same anatomic domain, it is rather intuitive that factors that lead to inflammation and cellular dysfunction should result in changes to both portions of the organ. Contrary to the restrictive and ossified understanding of PPDM in the past though, numerous high-quality studies since 2014 breathed new life into PPDM by showing that the primary pathological process in the exocrine pancreas should not necessarily be of gargantuan proportions to set the endocrine portion on the path to diabetes. With this fundamental shift in perspective and a whole new way of looking at the interaction between the endocrine and exocrine pancreas (81, 82, 83), PPDM is about to enter prime time. Because this type of diabetes is secondary, much PPDM is, in principle, preventable or treatable early at its root cause. However, there is a considerable risk for people with PPDM to fall through the cracks in the healthcare system as numerous healthcare professionals (not only endocrinologists but also gastroenterologists, surgeons, primary care physicians, radiologists, dietitians, nurses) are involved in their management. Accumulating data from various regions of the world (Australasia, Western Europe, Asia, Middle East, North America) speak to the need for cross-disciplinary evidence-based guidelines and tailored strategies to better manage this distinct, high-risk population of people with diabetes.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review. The author is the Principal Investigator of the COSMOS group.

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