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LEADING ARTICLE

Diabetes of the Exocrine Pancreas: Implications for Pharmacological Management

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Abstract

Post-pancreatitis diabetes mellitus, pancreatic cancer-related diabetes, and cystic fibrosis-related diabetes are often underappreciated. As a result, a substantial proportion of people with these sub-types of diabetes receive antidiabetic medications that may be suboptimal, if not harmful, in the context of their underlying disease of the exocrine pancreas. The present article delineates both classical (biguanides, insulin, sulfonylureas, α-glucosidase inhibitors, thiazolidinediones, and meglitinides) and newer (glucagon-like peptide-1 receptor agonists, amylin analogs, dipeptidyl peptidase-4 inhibitors, sodium-glucose co-transporter-2 inhibitors, D2 receptor agonists, bile acid sequestrants, and dual glucagon-like peptide-1 receptor and glucose-dependent insulinotropic polypeptide receptor co-agonists) therapies and provides recommendations for managing people with diabetes of the exocrine pancreas based on the most up-to-date clinical evidence. Also, several emerging directions (lipid-enriched pathways, Y4 receptor agonism, glucagon-like peptide-1 and glucagon receptor co-agonism) are presented with a view to informing the process of new drug discovery and development.

Key Points

Patients with diabetes of the exocrine pancreas (DEP) require individualized treatment plans.

Insulin as first-line treatment of DEP might suit only a minority of patients.

Early appropriate management of DEP has the potential to meaningfully reduce the burden of this type of diabetes.

1 Introduction

The present availability of 13 classes of glucose-lowering drugs is a great boon to management of diabetes mellitus. However, it comes at the time when the heterogeneity of the disease is increasingly recognized. One facet of this heterogeneity is diabetes of the exocrine pancreas (DEP), which is frequently misclassified as either type 2 or type 1 diabetes. Diabetes of the exocrine pancreas encompasses post-pancreatitis diabetes mellitus (PPDM, including diabetes after acute [PPDM-A] or chronic [PPDM-C] pancreatitis), pancreatic cancer-related diabetes (PCRD), and cystic fibrosis-related diabetes (CFRD) (Fig. 1). The incidence of DEP is projected to reach 16 per 100,000 general population by 2050, with an average annual growth of nearly 3% [1]. Comprehensive recommendations on diagnosis and classification of DEP were recently published elsewhere [2]. Acute pancreatitis, chronic pancreatitis, pancreatic cancer, and cystic fibrosis are discrete entities, and therefore it comes as no surprise that the diabetes that develops secondary to them may involve different pathogenetic pathways, with deep implications for both optimal pharmacotherapy of patients today and new drugs for diabetes tomorrow. Also, the modern paradigm of person-centered pharmacotherapy requires health care professionals to appreciate an array of comorbidities that diabetes patients may have. Therefore, knowledge of the advantages and disadvantages of major classes of glucose-lowering drugs is important. The above aspects prompted the authors to review human studies of classical, newer, and emerging therapies specifically in the context of DEP.

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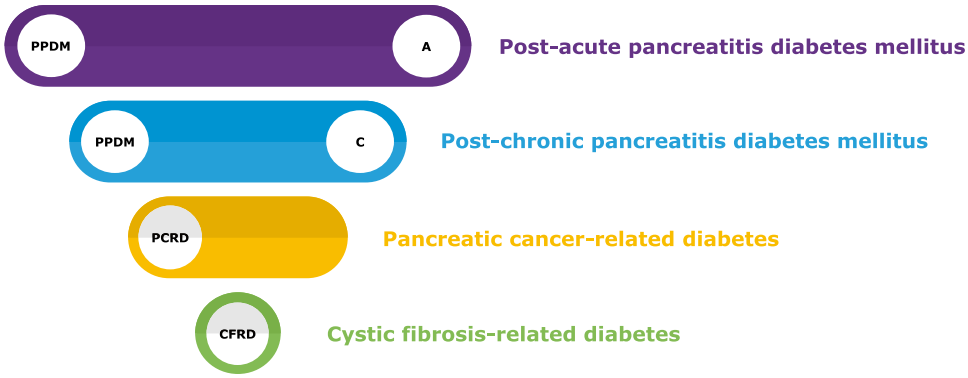

Fig. 1 Sub-types of DEP. The sub-types are arranged according to their frequency in the general population. *DEP* diabetes of the exocrine pancreas

2 Key Pharmacological Management Considerations

Management of DEP using drugs approved for type 1 and type 2 diabetes has been carried out using principles learned from treatment of the latter two types of diabetes. Except for CFRD, there have been no randomized controlled trials to inform either choice of antidiabetic agent or treatment targets specifically in DEP. Of note, landmark trials such as the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study (UKPDS), which established the benefit of glucose control in type 1 and type 2 diabetes, respectively, excluded individuals with DEP [3, 4]. Exclusion of DEP from diabetes trials has unfortunately been the norm for all major diabetes drug trials, including those of incretin-based agents.

Metformin and insulin have been the most commonly used drugs in DEP, which is consistent with several recent expert recommendations [5–10], while other guidelines continue to emphasize insulin alone [11]. Initial use of metformin or insulin has also been recommended for DEP associated with hereditary pancreatitis—generally considered to be a sub-type of chronic pancreatitis [12]. Of note, insulin remains the main recommended treatment for CFRD [13]. Selection of metformin or insulin as the initial agent is often based on individual patient features. Metformin is a reasonable first choice for patients with mild hyperglycemia and insulin resistance, whereas insulin is preferable for severe hyperglycemia, particularly in the setting of insulin deficiency and in patients with severe malnutrition (given its anabolic effects) [8]. Studies specifically in CFRD have found a beneficial effect of insulin to improve body mass index (BMI) [14].

Experts have recommended insulin as first-line treatment for DEP in children with chronic pancreatitis and recurrent acute pancreatitis, given that this addresses the primary deficit of insulin deficiency [15]. In a cohort of 397 children with acute recurrent pancreatitis or chronic pancreatitis, 24 had a physician diagnosis of diabetes, and 20 were treated with insulin [16]. Metformin may be considered in children with DEP and milder degrees of hyperglycemia who have features of insulin resistance such as obesity or acanthosis nigricans [15].

The progressive nature of DEP, especially associated with advanced chronic pancreatitis, often warrants treatment intensification, such that many patients initially controlled with metformin may ultimately require insulin once insulin deficiency develops. For example, a patient with PPDM-A who goes on to develop recurrent acute or chronic pancreatitis may also experience worsening glucose tolerance, necessitating changes in their antidiabetic regimen [17]. In a case series of 38 patients with DEP (6 associated with pancreatic cancer and 32 with benign pancreatic disease), metformin alone was the most common initial treatment, but 30 of the 38 patients required insulin within 12 months of diagnosis [18]. Whether to discontinue the metformin upon insulin initiation is based on the individual patient profile. Experts have recommended continuing metformin when possible to allow a lower dose of insulin and possibly to mitigate any carcinogenic effects of insulin [10].

There are even scenarios when treatment should be de-intensified. Many patients with DEP may have "brittle" diabetes, characterized by rapid fluctuations between hypoglycemia and hyperglycemia. Factors promoting hypoglycemia include loss of glucagon, carbohydrate malabsorption, unpredictable eating patterns (due to nausea or abdominal pain) and preserved peripheral insulin sensitivity. Hyperglycemia may be promoted by deficiency of insulin and pancreatic polypeptide that increases hepatic glucose production [7, 19]. The glycemic target for patients at high risk for hypoglycemia should not be strict (i.e., the usual hemoglobin A1c target of less than 7% may be inappropriate). Another setting where flexibility of therapy may be needed concerns patients with PCRD on antidiabetic therapy who undergo surgery or chemotherapy, which may improve (or even normalize) glucose intolerance [6].

Beyond insulin and metformin, other antidiabetic medications have scarcely been studied. Given that 45–90% of cases of DEP are misclassified as having type 2 diabetes [20, 21], a

substantial proportion of these patients have been prescribed antidiabetic medications that may be inappropriate or even unsafe given the underlying disease of the exocrine pancreas.

3 Classical Therapies

Biguanides, insulin, sulfonylureas, thiazolidinediones, and meglitinides were first used for treatment of diabetes in the 20th century and therefore represent classical therapies (Fig. 2).

3.1 Biguanides

Several observational cohort studies have suggested an antineoplastic effect of metformin. Diabetes and chronic pancreatitis alone are associated with an increased risk of pancreatic cancer (with an especially high risk if both are present) and are integral parts of clinical prediction models for pancreatic cancer [22]. Therefore, any effect of metformin to prevent pancreatic cancer would be of great value. A systematic review and meta-analysis of 10 cohort studies and 3 case–control studies found metformin use in type 2 diabetes was associated with a reduced risk of pancreatic cancer (risk ratio [RR] 0.62, 95% confidence interval [CI] 0.46–0.86), with no evidence of publication bias [23]. In contrast, another systematic review and meta-analysis of 6 cohort studies, 3 case–control studies (these 9 observational studies were also included in the meta-analysis described above), and 2 randomized controlled trials concluded that metformin was not associated with reduced risk of pancreatic cancer [24]. Thus, despite much interest in a protective effect of metformin against pancreatic cancer, sparked by the first study nearly 15 years ago [25], this effect of metformin is uncertain at present. It might also reflect preferential use of metformin in patients with less severe diabetes, with such diabetes possibly conferring a lower risk of pancreatic cancer. Of note, even if metformin does have antineoplastic effects, to date it has been studied in cohorts of type 2 diabetes, lending uncertainty regarding whether the benefit would also be seen in DEP, given the potential differences in pathophysiology between the two types of diabetes and up to 7-times higher risk for pancreatic cancer in PPDM versus type 2 diabetes [26].

Several studies have examined the potential impact of metformin in the setting of PCRD. A meta-analysis of 21 studies (including over 38,000 patients) found that metformin use in patients with diabetes and pancreatic cancer was associated with a survival benefit compared to metformin non-users (hazard ratio [HR] 0.83, 95% CI 0.74–0.91), with lower mortality observed for early and mixed stage cancer but not advanced stage cancer [27]. This analysis consisted of 19 cohort studies and 2 randomized controlled trials. These randomized trials found no benefit of adding metformin to chemotherapy regimens in patients with advanced/metastatic pancreatic cancer [28, 29]. Whether metformin will have a role as adjunctive therapy in earlier stages of pancreatic cancer will require purposely designed randomized controlled trials. Nevertheless, these data do shed positive light on metformin as treatment in DEP.

Using nationwide pharmaceutical and hospital discharge data in New Zealand, the Clinical and epidemiOlogical inveStigations in Metabolism, nutritiOn, and pancreatic diseaseS (COSMOS) program studied the relationship between

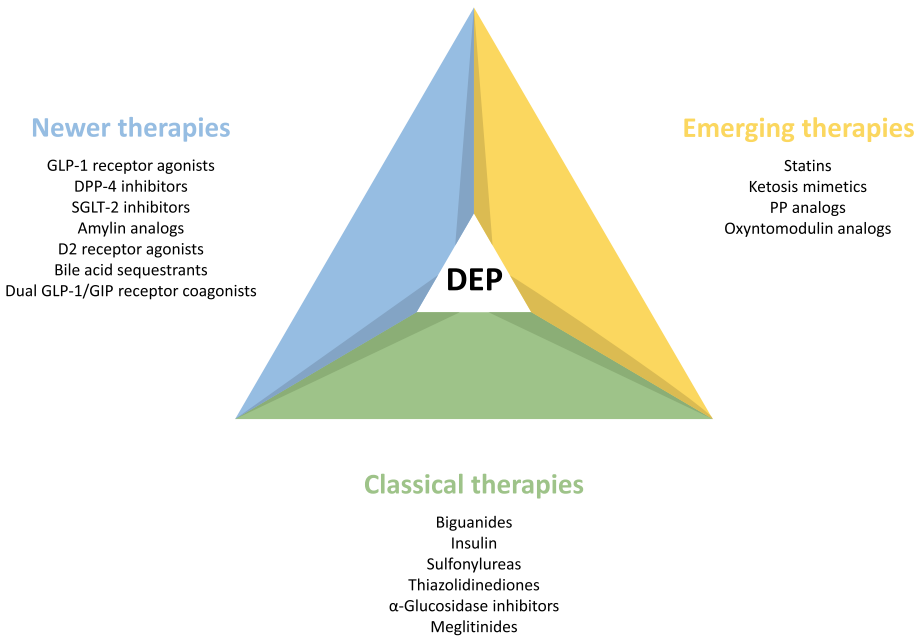

Fig. 2 Concept map of pharmacological management of DEP. *DEP* diabetes of the exocrine pancreas, *DPP-4* dipeptidyl peptidase-4, *GIP* glucose-dependent insulinotropic polypeptide, *GLP-1* glucagon-like peptide-1, *SGLT-2* sodium-glucose co-transporter-2, *PP* pancreatic polypeptide

antidiabetic drug use and mortality in 836 individuals with PPDM and 1026 with PCRD [30]. Compared to those with PPDM who never used antidiabetic agents, first-use of metformin monotherapy was associated with lower mortality (adjusted HR 0.22, 95% CI 0.09–0.53) as was ever-use of metformin (HR 0.51, 95% CI 0.36–0.70). A greater mortality benefit with metformin use in PPDM versus type 2 diabetes was also observed (adjusted HR 0.75, 95% CI 0.72–0.77) [30]. A clear survival benefit of metformin in PCRD was not seen in this study. Despite the potential benefits of metformin in DEP, a Danish nationwide cohort study found that only 64.5% of patients with PPDM had ever received a prescription for metformin, which was significantly lower (RR 0.85, 95% CI 0.83–0.86) than the 76.3% rate of metformin prescription in those with type 2 diabetes [20]. The above-mentioned COSMOS population-based cohort study found that 59.6% of patients with PPDM had ever received a prescription for metformin as compared with 74.1% of those with type 2 diabetes [30].

In the Diabetes Prevention Program, metformin reduced the incidence of diabetes by 31% in participants with impaired glucose tolerance [31]. Whether metformin can prevent diabetes in patients with a history of disease of the exocrine pancreas warrants study, especially in chronic pancreatitis where the risk of developing diabetes increases with increasing duration of disease (4%–10% at onset of chronic pancreatitis, 28–50% at 10 years, and 52–83% by 20–25 years) [32, 33]. Given that the risk of developing new-onset diabetes begins to increase early after clinical resolution of pancreatitis [34] and is up to 25% 5 years after an episode of acute pancreatitis [35, 36], trials evaluating metformin prevention in this setting are also needed. Instruments for identifying individuals at high risk for diabetes after acute pancreatitis [37] or after chronic pancreatitis [38] will be of high value for selecting participants for diabetes prevention trials.

Potential drawbacks of metformin use in DEP include side effects such as bloating, abdominal discomfort, and diarrhea. While this will not be problematic for patients with DEP associated with resolved mild acute pancreatitis, these side effects may be less tolerable with those with DEP secondary to chronic pancreatitis or pancreatic cancer. Such side effects may be avoided by gradual dose titration. Metformin also has a mild effect to promote weight loss, which would be problematic only for patients with DEP with severe malnutrition. Metformin is associated with a rare but dangerous side effect of lactic acidosis, which is a concern for patients with renal insufficiency or ongoing alcohol abuse. Given that patients with PPDM may have an increased risk of hospitalization for chronic kidney disease [39], renal function should be assessed before prescribing metformin.

3.2 Insulin

Multiple meta-analyses of prospective studies have found that around 25% of individuals with acute pancreatitis developed diabetes, of which about 70% received insulin treatment [35, 36]. Similarly, meta-analyses have found an incidence rate of 30% of new-onset diabetes after chronic pancreatitis, the majority of whom received insulin [40]. After both acute and chronic pancreatitis, rates of insulin-treated diabetes increases with increasing duration after diagnosis of pancreatitis [35, 36, 40]. Given that no clinical trials have been performed to specifically recommend insulin, the widespread use of insulin in DEP likely reflects several factors, including (a) the assumption that insulin deficiency is the key deficit across all sub-types of DEP, (b) earlier expert recommendations that insulin should be used as first-line treatment in DEP (assuming poor or transient response to oral antihyperglycemic agents) [41, 42], and (c) the severity of hyperglycemia in DEP, especially long-standing, often requires insulin for glycemic control.

Several studies have documented a more frequent prescription of insulin therapy in individuals with DEP compared to those with type 2 diabetes. Despite higher rates of insulin use, glycemic control is often worse, reflecting the difficulty in achieving treatment success in DEP [21, 43]. Uncontrolled hyperglycemia in DEP leading to insulin initiation or poor glycemic control that persist despite use of insulin are both possible. In addition, rates of hypoglycemia are uniformly greater in DEP versus type 2 diabetes [43–45]. Studies of large national databases have been particularly informative in this regard. The first study of this kind identified (using Read codes, which are similar to ICD codes) 31,789 cases of newly diagnosed diabetes among over 2 million adults seen in primary care practices in the United Kingdom (2005 to 2016), of which 559 (1.8%) occurred after pancreatic disease and were deemed DEP [21]. These consisted of 361 cases (65%) of PPDM-A and 198 cases (35%) associated with chronic pancreatic disease (91 cases of PPDM-C, 11 cases of PCRD, 18 cases of CFRD, and 78 other cases). Most of the cases (30,876 or 97% of the incident cases) were deemed type 2 diabetes and 354 cases (1.1%) were diagnosed as type 1 diabetes. Compared to type 2 diabetes, DEP was associated with higher likelihood of initiation of insulin therapy within 1 year and within 5 years of diagnosis, with and without adjustment for baseline characteristics (Table 1).

A nationwide population-based cohort study based on South Korea's National Health Insurance Service (ICD-10 codes and pharmacy data, focused on adults with newly diagnosed diabetes from 2012 to 2017) compared 153,894 patients with type 2 diabetes (defined as diabetes without prior pancreatic disease) to 3629 cases of DEP (diabetes with a prior diagnosis of pancreatic disease) [44]. The group

Table 1 Incidence of insulin use after the diagnosis of different types of diabetes in national databases

Type of diabetes	Setting	Insulin use at 1 year			Insulin use at 5 years		
		Incidence	Unadjusted odds/hazard ratio	Adjusted* odds/hazard ratio	Incidence	Unadjusted odds/hazard ratio	Adjusted* odds/hazard ratio
Type 2 diabetes	UK	1.4%	1.0	1.0	4.1%	1.0	1.0
Type 2 diabetes	South Korea	10.8%	1.0	1.0	19.3%	1.0	1.0
DEP overall	UK	16.3%	13.5 (10.3–17.5)	9.6 (7.0–13.2)	29.6%	9.9 (7.2–13.4)	7.4 (5.2–10.4)
DEP overall	South Korea	17.8%	1.71 (1.58–1.85)	1.39 (1.29–1.51)	32.4%	1.63 (1.54–1.73)	1.38 (1.30–1.47)
PPDM-A	UK	9.7%	7.5 (5.0–10.9)	6.4 (4.1–9.7)	20.9%	6.2 (4.0–9.3)	5.2 (3.3–8.2)
DEP other than PPDM-A	UK	28.9%	28.3 (19.6–40.2)	16.4 (10.4–25.6)	45.8%	19.8 (12.3–31.7)	12.9 (7.4–22.2)

*The UK study adjusted for age, sex, ethnicity, index of multiple deprivation score, smoking status, and BMI. The South Korean study adjusted for age, sex, BMI, fasting plasma glucose, LDL cholesterol, alcohol consumption, smoking status, medical coverage, systolic blood pressure, triglycerides, eGFR, and Charlson comorbidity index

BMI body mass index, *eGFR* estimated glomerular filtration rate, *DEP* diabetes of the exocrine pancreas, *LDL* low-density lipoprotein, *PPDM-A*, post-pancreatitis diabetes mellitus including diabetes after acute pancreatitis

with DEP consisted of PPDM-A (28.4%), PPDM-C (62.4%), PCRD (9.0%) and CFRD (0.2%). The primary outcome—incidence of initiation of insulin therapy—was significantly greater in DEP versus type 2 diabetes (Table 1). Insulin use rates were higher across all categories in this study in comparison to the United Kingdom study described above [21]. Diabetes of the exocrine pancreas, in comparison to type 2 diabetes, was associated with higher rates of hypoglycemia (adjusted odds ratio [OR] 1.85, 95% CI 1.54–2.21), microvascular complications, macrovascular complications, and all-cause mortality.

Another nationwide population-based cohort study collected 398,456 cases of new-onset diabetes in adults in Denmark from 2000 to 2018 (used ICD-10 codes and prescription data) [20]. This study focused on PPDM and therefore excluded PCRD and CFRD. Most patients were classified as having type 2 diabetes (96.2%) while 2.3% were classified as type 1 diabetes and 1.5% as PPDM (0.9% PPDM-A and 0.6% PPDM-C). Unlike the studies described above, this study not only described insulin use but also examined use of non-insulin antidiabetic therapies (discussed below). Once again, an earlier and increased use of insulin was observed in PPDM compared to type 2 diabetes. Over a median follow-up of 6.7 years, the overall adjusted HR for insulin use was 3.10 (95% CI 2.96–3.23) in the entire PPDM group, 2.45 (95% CI 2.30–2.61) in those with PPDM-A, and 4.30 (95% CI 4.05–4.56) in those with PPDM-C. The frequency of insulin prescription was 17.8% in type 2 diabetes and 42.5% in PPDM.

A comparison of metabolic features between 142 individuals with DEP (diabetes occurring after pancreatitis or pancreatic surgery) and 142 individuals with type 2 diabetes matched for age, sex, and duration of diabetes [43] found that those with DEP received insulin more frequently (OR 4.2, 95% CI 2.6–6.9) and had higher hemoglobin A1c levels (9.0% vs 8.1%) and more episodes of hypoglycemia (46% vs 18%) [43]. Another study compared 78 patients with PPDM to 5486 patients with type 2 diabetes; the rates of insulin therapy were 21.8% and 5.1%, respectively, with a non-significant trend for higher hemoglobin A1c levels in those with PPDM [46].

Insulin is often used in patients with hereditary pancreatitis who develop diabetes. Among 5 members of a family with a mutation (N29T) in the *PRSS1* gene, all members ultimately required insulin therapy, though 4 of them used metformin and glyburide (mean 46 months) prior to initiating insulin [47]. Glycemic control was poor (mean hemoglobin A1c 9.9%, with frequent hyperglycemia and hypoglycemia) [47]. The type of mutation may dictate the need for insulin treatment. In a case series of patients with pancreatitis, among 32 patients with an intronic variant in *PRSS1*, only 3 developed diabetes (which was controlled with metformin). In contrast, among 52 patients with exonic variants, 27 developed diabetes, of whom 40% were treated with insulin [48].

It has been recommended that insulin dosing in DEP should follow practices for type 1 diabetes, given the predominant insulin deficient state and relatively preserved insulin sensitivity; however, higher doses may be needed for overweight patients. A study that matched patients with DEP with patients with type 1 or type 2 diabetes found that insulin doses were similar between type 1 diabetes and DEP (0.60 to 0.62 units/kg/day) and lower in those with type 2 diabetes (0.56 units/kg/day) [45].

Insulin may be administered by single or multiple daily injections (MDI) or via continuous subcutaneous insulin infusion (CSII) via insulin pump. Few studies have compared the methods of insulin delivery in patients

with DEP. In a study of 39 patients with a history of total pancreatectomy and insulin-dependent DEP, 18 patients were treated with CSII and 21 with MDI [49]. A trend for lower hemoglobin A1c (8.1% vs 7.3%, $p = 0.16$) was observed for CSII compared to MDI. In a 1-month period, rates of severe hypoglycemia (glucose < 50 mg/dL) were significantly lower with CSII than MDI (17% vs 52%, $p = 0.02$). Additional and larger studies, with inclusion of PPDM, PCRD, CFRD, will be needed to fully establish the superiority of CSII in treatment of DEP. In the meantime, it is reasonable to use CSII in insulin-deficient DEP patients with sufficient motivation, especially those who eat multiple small meals [7]. Future technologies such as a bi-hormonal artificial pancreas (delivering insulin and glucagon) with closed-loop glucose control showed promise in a study of 12 patients who had undergone total pancreatectomy, finding increased time in euglycemia and reduced time in hypoglycemia compared to current diabetes care [50].

In the COSMOS nationwide database study described above, insulin therapy was neutral in terms of mortality risk in DEP [30]. Observational studies have associated insulin use with pancreatic cancer [51, 52]. However, whether this reflects a causal effect of insulin is not established. It is possible that the relationship is confounded by the known relationship between diabetes itself and pancreatic cancer [53]. Those who require insulin may have more severe hyperglycemia, which may increase the risk of pancreatic cancer, rather than the insulin treatment. Of note, short-term insulin use has been associated with an increased risk of pancreatic cancer, whereas long-term use has been associated with neutral or reduced risk of pancreatic cancer [54–56]. That insulin treatment is generally given long term might mitigate against risk of pancreatic cancer. Administration of insulin to a patient with DEP should be done only when control of significant hyperglycemia is deemed to have a higher benefit than the theoretical risk of pancreatic cancer. Moreover, a COSMOS study found that long-term insulin use (vs never use) after a first attack of acute pancreatitis was associated with a higher risk of progression to recurrent acute or chronic pancreatitis (adjusted HR 1.56, 95% CI 1.15–2.11) [57]. Thus, insulin should be considered especially carefully for the subset of patients with PPDM-A, many of whom (diabetes after non-necrotizing acute pancreatitis) have a better likelihood of milder diabetes that could be controlled with metformin versus the more severe forms of DEP that often require insulin.

3.3 Sulfonylureas

Sulfonylureas act by stimulating insulin release from pancreatic β cells. A European guideline on the management of chronic pancreatitis recommended against the use of sulfonylureas in DEP given the risk of hypoglycemia [8]. An American guideline stated that sulfonylureas could be used in early PPDM-C with mild hyperglycemia but encouraged use of short-acting agents to avoid hypoglycemia [7]. Hypoglycemia with sulfonylureas is particularly concerning given that several studies have documented high risk of hypoglycemia in DEP [43–45, 58]. The nationwide Danish population-based cohort study described above found that 25% of those with PPDM had received a prescription of sulfonylureas [20]. With the advent of newer therapies (described below), the use of sulfonylureas in type 2 diabetes has been decreasing in recent years. However, the Danish study found that this decrease occurred two years later in patients with PPDM compared to those with type 2 diabetes [20]. Given the dependence of sulfonylurea action on functional β cells and the risk of hypoglycemia, sulfonylureas are not optimal treatment in most cases of DEP, regardless of the underlying etiology.

3.4 Thiazolidinediones

Thiazolidinediones improve glycemia by improving peripheral insulin sensitivity. Experts have recommended against use of thiazolidinediones in DEP given their association with bone fractures, fluid retention, and congestive heart failure [7, 8]. The association with fractures is a particular concern given that individuals with chronic pancreatitis have an increased risk of osteoporosis [59]. Although primarily known as a peripheral insulin sensitizer, thiazolidinediones may also improve hepatic insulin sensitivity, which has been documented in PPDM-C [60]. Given that insulin resistance has been observed in PPDM-A, PPDM-C, and PCRD [61–63], clinical trials of these agents in patients with these conditions are needed to demonstrate whether the benefits outweigh the risks.

3.5 Other Classes

α-Glucosidase inhibitors (e.g., acarbose, miglitol), which improve glycemia by delaying glucose absorption, have been recommended against in DEP as they may exacerbate exocrine insufficiency and have prominent gastrointestinal adverse effects (flatulence, diarrhea, bloating, abdominal pain) [8]. In addition, patients on these agents who have a hypoglycemic event must take glucose rather than sucrose—another potential disadvantage given higher risk of hypoglycemia in DEP. Meglitinides (e.g., repaglinide and nateglinide) are insulin secretagogues that have a similar mechanism of action as sulfonylureas but have a faster onset and shorter duration of action. At least one guideline has suggested they might be used early in DEP [8]. A relatively small (75 participants) open-label randomized trial in CFRD found repaglinide to be non-inferior to insulin in glycemic control [64].

However, given the dependence of these agents on intact β cells for efficacy and their risk of hypoglycemia, they are of low interest as treatment for DEP.

4 Newer Therapies

The main classes of drugs approved for clinical use in the 21st century include glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucose co-transporter-2 (SGLT-2) inhibitors (Fig. 2).

4.1 Incretin-Based Therapies

Incretin hormones (glucose-dependent insulinotropic polypeptide (GIP) secreted by K-cells in the small intestine and glucagon-like peptide-1 [GLP-1] secreted by L-cells in the ileum and large intestine) are secreted by the gut in response to food and augment insulin secretion when circulating glucose levels are elevated. Both GLP-1 and GIP are rapidly inactivated by DPP-4. Evidence suggests that there is deficient secretion of GLP-1 and resistance to GIP in type 2 diabetes [65]. The incretin system also appears to be dysfunctional in DEP [66–68]. However, in contrast to type 2 diabetes, where incretin-based agents (GLP-1 receptor agonists and DPP-4 inhibitors) have been used with increasing frequency, such agents are very rarely used in the treatment of properly diagnosed DEP, for safety concerns outlined below.

For patients with active pancreatic disease, the gastrointestinal effects of GLP-1 receptor agonists, such as nausea, early satiety, decreased appetite, and delayed gastric emptying, may be problematic. Glucagon-like peptide-1 receptor agonists have a well-recognized weight loss effect. Indeed, this effect is so significant that several GLP-1 receptor agonists have been approved as weight loss medications in people without diabetes (liraglutide, semaglutide). In patients with DEP who have exocrine pancreatic dysfunction (and the resulting nutritional deficiencies), this weight loss effect may be undesirable.

Several years ago, an alarm was raised that incretin-based agents (GLP-1 receptor agonists or DPP-4 inhibitors) could be linked to an increased risk of pancreatitis and pancreatic cancer, based on the US Food Drug Administration (FDA) adverse event reporting with the first two such agents, exenatide and sitagliptin [69]. Many subsequent studies examined these concerns. A challenge to determine whether a drug causes pancreatitis or pancreatic cancer in diabetes is the fact that diabetes itself appears to increase the risk of pancreatitis and pancreatic cancer [55].

Observational case-control and cohort studies, which are subject to various biases, yielded mixed results on whether GLP-1 receptor agonists increase the risk of pancreatitis or pancreatic cancer. Conclusions based on early trials of incretin-based agents were problematic due to poorly defined criteria for the diagnosis of pancreatitis; however, once this safety signal was publicized, more recent randomized trials have prespecified pancreatic disease as adverse events with specific criteria for detection [70]. Meta-analyses of these randomized controlled trials have been conducted to address the issue more clearly. A meta-analysis of 3 GLP-1 receptor agonist randomized clinical trials with 2 or more years of follow-up in which acute pancreatitis was a predefined and adjudicated adverse event (LEADER, ELIXA, and SUSTAIN-6, which studied liraglutide, lixisenatide, and semaglutide, respectively) found no increased risk of acute pancreatitis in the 9347 participants treated with GLP-1 receptor agonists versus 9353 treated with placebo (OR 0.75, 95% CI 0.47–1.17) [71]. More recently, a meta-analysis of 7 randomized trials (the 3 trials mentioned above plus EXSCEL, Harmony Outcomes, PIONEER 6, and REWIND, which studied exenatide, albiglutide, oral semaglutide, and dulaglutide, respectively), was conducted, encompassing 56,004 participants with type 2 diabetes with median follow-up ranging from 1.3 to 5.4 years [72]. The risk of acute pancreatitis was not increased, with 92 cases occurring in those treated with GLP-1 receptor agonists and 88 cases among controls (OR 1.05, 95% CI 0.78–1.40). Further, the risk of pancreatic cancer was also not increased, with 57 cases in the drug group and 51 cases in the placebo group (OR 1.12, 95% CI 0.77–1.63). Additional meta-analyses of these 7 randomized controlled trials also concluded that GLP-1 receptor agonists were not associated with increased risk of acute pancreatitis, pancreatic cancer (or any cancer for that matter) [73, 74]. Of note, while randomized controlled trials may not suffer from biases that confound observational studies, they do have the disadvantage of lasting for only a few years, which may limit the power to detect rare events (such as pancreatic cancer) that occur over a long period of time [70].

Meta-analyses have also been conducted to examine the risk of pancreatitis and pancreatic cancer with DPP-4 inhibitors. While such analyses have not confirmed a risk of pancreatic cancer, they have suggested an increased risk of acute pancreatitis [73, 74]. A meta-analysis of 4 randomized controlled trials (SAVOR TIMI 53, EXAMINE, TECOS, and CARMELINA, which studied saxagliptin, alogliptin, sitagliptin, and linagliptin, respectively) documented an increased risk of acute pancreatitis (OR 1.75, 95% CI 1.14–2.70) [73]. The authors noted that in each DPP-4 inhibitor trial, a non-significant increase in acute pancreatitis was observed, which was not the case in GLP-1 receptor agonist trials. A second meta-analysis documented a similar increased risk of acute pancreatitis when examining these 4 trials jointly (OR 1.79, 95% CI 1.17–2.72); the addition of active comparator trials (CAROLINA and OMNEON, which

studied linagliptin and omarigliptin) to the 4 trials also found a significant risk (OR 1.54, 95% CI 1.08–2.18) [74].

While patients with overt DEP due to chronic pancreatitis or pancreatic cancer have typically been excluded from clinical trials of antidiabetic therapy, the concern that incretin agents could increase the risk of pancreatitis led to essentially complete exclusion of DEP from recent clinical trials, including patients with a history of acute pancreatitis. As a result, any evidence-based benefit or harm of modern antidiabetic agents cannot be confidently extrapolated to DEP, despite reassurances from regulatory agencies [75]. Given that individuals with a history of a single attack of acute pancreatitis, recurrent acute pancreatitis, or chronic pancreatitis may have a 2-fold to 7-fold increased risk of pancreatic cancer [76–78], incretin-based agents should be avoided in DEP until clinical trials prove that they are safe in these patients. A Danish nationwide study that characterized adult cases of diabetes diagnosed from 2000 to 2018 found that DPP-4 inhibitors and GLP-1 receptor agonists were prescribed in 14.1% and 6.3% of patients with PPDM, respectively [20]. A European diabetes registry study found that 0.2–1.4% of patients with DEP were treated with GLP-1 receptor agonists and 0.2–6% were treated with DPP-4 inhibitors [45].

Recently, a dual GLP-1 and glucose-dependent insulinotropic peptide (GIP) receptor co-agonist, tirzepatide, has become available for the treatment of type 2 diabetes [79]. Tirzepatide appears to be more potent than GLP-1 receptor agonists in terms of glucose control and weight loss. The significant weight loss may be undesirable for patients with DEP who have exocrine pancreatic dysfunction. Tirzepatide is associated with gastrointestinal side effects similar to GLP-1 receptor agonists (described above). Given that patients with a history of pancreatitis were excluded from clinical trials of tirzepatide, their role in treatment of DEP remains to be determined. A critical unknown is whether the additional GIP receptor agonism would increase the risk of pancreatitis or pancreatic cancer in patients with a history of pancreatitis.

Until appropriate trials are completed to demonstrate safety of incretin-based agents in DEP, what can be done to improve incretin function in DEP? A leading hypothesis is that impaired nutrient absorption due to exocrine pancreatic dysfunction arising in pancreatic disease contributes to impaired incretin secretion and therefore reduced postprandial insulin secretion in DEP; however, evidence is mixed in this regard [80–83]. If this is the case, it would suggest that pancreatic enzyme replacement therapy to optimize nutrient digestion may improve glycemia via improved incretin response. Only a few small studies have administered pancreatic enzymes in the setting of PPDM-C and CFRD; while post-meal incretin levels did increase, glycemic improvement was not consistently observed [80, 82, 84, 85]. Further studies are needed.

Priority for clinical trials in DEP should be for GLP-1 receptor agonists, given that they have had positive results in cardiovascular outcome trials and are protective against albuminuria [86]. On the other hand, while DPP-4 inhibitors have few side effects, the uncertainty regarding their risk of pancreatitis and the lack of demonstrated cardiovascular benefit make these agents low priority for clinical trials in patients with DEP. At this time, cardiovascular outcome trials have not been published for tirzepatide. If such trials eventually demonstrate cardioprotective effects of tirzepatide that would justify clinical trials of this novel agent in DEP.

4.2 SGLT-2 Inhibitors

SGLT-2 inhibitors lower blood glucose by reducing renal glucose and sodium reabsorption, increasing urinary glucose excretion. SGLT-2 inhibitors have been associated with euglycemic diabetic ketoacidosis, particularly in type 1 diabetes. Given that DEP is often an insulin-deficient state, experts have recommended against their use in DEP until trials are performed to demonstrate their safety [8]. This caution pertains mainly to people with PPDM-C and may be less of a concern for patients with PPDM-A. SGLT-2 inhibitors also induce weight loss, which may be undesirable for some patients suffering from pancreatic disease. On the other hand, SGLT-2 inhibitors have been found to have multiple non-glycemic benefits, including protection against cardiovascular events and an effect to preserve renal function [87]. Another attractive aspect of SGLT-2 inhibitors for DEP is that their mechanism of action does not depend on insulin production or response, such that they may retain glycemic effectiveness even in patients with advanced chronic pancreatitis. Clinical trials are warranted to evaluate SGLT-2 inhibitors for DEP. Patients best suited for enrollment in such clinical trials would be those with PCRD, PPDM-A or early PPDM-C without insulinopenia, given that insulin deficiency may increase the risk of euglycemic ketoacidosis. Patients with malnutrition would also be unsuitable given the potential weight loss effect of SGLT-2 inhibitors.

4.3 Other Classes

Amylin, which is co-secreted with insulin, slows gastric emptying, suppresses postprandial glucagon secretion, decreases hepatic glucose output, and increases satiety. Pramlintide, an amylin analog, was approved in the USA for use in type 1 and type 2 diabetes. Given its mild improvement in glycemic control and high rates of nausea, vomiting, anorexia, and headache, it is rarely used in general and is a poor candidate for treatment of DEP. Another concern is that pramlintide increases the risk of hypoglycemia when used with insulin, and many patients with DEP are prescribed insulin. The frequent gastrointestinal side effects associated

with rapid-acting D2 receptor agonists (e.g., bromocriptine) and bile acid sequestrants (e.g., colesevelam)—both approved as treatments for diabetes in the USA—preclude their use in patients with DEP, in whom these drugs have not been well studied.

5 Emerging Therapies

Research advances have enabled clinical trials of several novel compounds in individuals with diseases of the exocrine pancreas [88–90]. At present, the directions closest to clinical translation in DEP are lipid-enriched pathways, Y4 receptor agonism, and GLP-1/glucagon receptor co-agonism (Fig. 2).

5.1 Lipid-Enriched Pathways

The pathways regulating glucose and lipid metabolism are closely intertwined. However, derangements of lipid metabolism in the context of DEP have been scarcely investigated to date. A 2017 COSMOS study was the first to investigate lipid metabolism specifically in individuals with PPDM [91]. It showed that when compared with individuals with normoglycemia after an attack of acute pancreatitis, individuals with PPDM had significantly higher fasting levels of triglycerides. This was independent of age, sex, BMI, and severity of acute pancreatitis. Similarly, circulating levels of glycerol—an important intermediate of glucose and lipid metabolism involved in the processes of glycogenesis and gluconeogenesis—were significantly elevated in individuals with PPDM. A subsequent COSMOS study demonstrated that glycerol was significantly directly associated with β-hydroxybutyrate whereas triglycerides were inversely associated with acetoacetate, suggesting that ketosis is involved in PPDM [92]. At the same time, fasting insulin and homeostatis model assessment of insulin resistance (HOMA-IR) were not associated with any marker of lipid metabolism in this population, suggesting that insulin resistance is not a major driver of dyslipidemia in PPDM [91]. A 2020 metabolomics study sought biomarkers in serum that distinguish DEP from type 2 diabetes [93]. Notably, of the 5 identified biomarkers, 4 belonged to lipids. Another 2020 study found that dyslipidemia is significantly associated with the presence of diabetes in patients with chronic pancreatitis [94]. A 2023 machine learning study of routinely collected hospital data identified low circulating levels of high-density lipoprotein cholesterol at the time of hospitalization for first attack of acute pancreatitis as a significant predictor of PPDM-A after hospital discharge [95].

Therapeutic implications of targeting lipid-enriched pathways in PPDM were empirically confirmed in a 2023 pharmacoepidemiological study from the USA [96]. The use of statins (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor) in individuals (who had no pre-existing diabetes) after a first attack of acute pancreatitis was associated with a statistically significant reduction in the risk of PPDM among statin users during a median follow-up of 3.5 years in comparison with non-users. The risk reduction ranged between 15% among irregular users and 42% among regular users. Notably, the study did not find a linear dose-response relationship, suggesting that a low dose of statin may suffice for the purpose of prevention of PPDM. It is worth acknowledging that the FDA added a safety warning to statin labels in 2012 to call attention to the slightly increased risk of type 2 diabetes in people receiving statins [97]. While future studies will unveil the exact mechanism underlying the beneficial role of statins in PPDM, the differential effect of statins on PPDM versus type 2 diabetes reinforces the notion that PPDM has unique basic elements of the pathogenesis.

The other recently discovered way to therapeutically manipulate lipid-enriched pathways in individuals after acute pancreatitis is via ketogenesis. The CETUS randomized controlled trial (as part of the COSMOS program) investigated the acute effects of oral ketone monoester on a range of metabolic parameters in individuals with new-onset prediabetes after acute pancreatitis. The ingestion of D-β-hydroxybutyrate-(R)-1,3 butanediol led to markedly elevated circulating levels of β-hydroxybutyrate and resulted in significantly reduced levels of triglycerides and glucose [98, 99]. The pharmacological developments described above are well in line with the growing appreciation of intra-pancreatic fat deposition (as the local source of lipids in the pancreas), not merely general obesity, in diseases of the pancreas [100].

5.2 Y4 Receptor Agonism

The pancreatic polypeptide (PP) family is one of the most phylogenetically conserved families of regulatory peptides. It comprises neuropeptide Y, peptide YY, and PP—all consisting of 36 amino acids and found in different locations throughout the body. Of these, PP—secreted by the γ cells in the pancreas and preferentially bound to the Y4 receptor in humans—has long been hypothesized to play a role in the pathogenesis of DEP. In the 1970s, PP was suggested to be a biomarker of advanced chronic pancreatitis (and the diabetes that accompanies it). This was based on the observation that the number of γ cells was markedly increased in chronic pancreatitis and was attributed to the loss of β cells [101]. Also, PP was suggested to be a biomarker of pancreatic cancer (located in the proximal portion of the pancreas) because, while γ cells contribute less than 5% to the total pancreatic islet cell mass, γ cell rich regions were found in the uncinate process of the pancreas in which γ cells contribute to over 50% of the islet cell mass [102, 103]. Several human studies in the 1980s showed significantly reduced levels of

PP in individuals with chronic pancreatitis (many of whom also had PPDM) in comparison with healthy controls [104, 105]. There has recently been a rekindled interest in this peptide, more specifically the use of PP response to a mixed meal as a biomarker of DEP. A 2022 study (48 individuals included) from China found no significant difference in terms of postprandial levels of PP between individuals with PPDM-C and type 2 diabetes [106]. Further, among individuals with chronic pancreatitis, those with normoglycemia had significantly lower levels of PP than individuals with PPDM. By contrast, a 2023 study (165 individuals) from the USA showed significantly lower fasting and postprandial levels of PP in individuals with diabetes in the context of chronic pancreatitis in comparison with type 2 diabetes [107]. Similarly, individuals with PCRD had significantly lower postprandial levels of PP than individuals with type 2 diabetes in a small pilot study [108].

Studies to date have predominantly investigated the Y1 receptor (to which neuropeptide Y predominantly binds), which is known to promote inflammation in the gastrointestinal tract. By contrast, the Y4 receptor that preferentially binds PP and therapeutic exploitation of its agonism in humans has received little attention. A 1988 study in patients who had undergone pancreatic resection for trauma showed that intravenous PP administration reversed the hepatic insulin resistance in PP-deficient individuals in comparison with healthy volunteers [109]. A 1996 clamp study by the same group showed that intravenous PP administration reversed the hepatic insulin resistance and improved glycemic control in individuals with chronic pancreatitis in comparison with lean healthy volunteers [63]. A limitation of native PP as a potential therapeutic agent is its rapid degradation and short circulating half-life. However, this does not appear to be an insurmountable issue given that a DPP4-resistant PP analog was well tolerated by study participants in a Phase I trial [110].

5.3 GLP-1/Glucagon Receptor Co-agonism

Containing the entire sequence of glucagon (as well as an octapeptide extension), oxyntomodulin is a homolog of this pancreatic hormone that is secreted in the distal gut and brainstem. The 2 hormones are a result of differential post-translational processing of proglucagon by tissue-specific prohormone convertases. Oxyntomodulin has affinity for both the GLP-1 receptor and glucagon receptor, although lower in comparison with their cognate peptides. In the human pancreas, the GLP-1 receptor is expressed on both the islets of Langerhans and acinar cells, whereas the glucagon receptor is expressed on the former only [111, 112]. A notable acute glucose-lowering (independent of weight reduction) effect of native oxyntomodulin in humans was first reported in 2018 [113]. Perhaps more importantly, that study debunked the earlier belief of worsening blood glucose control following administration of oxyntomodulin due to the effect of the glucagon receptor activation. While the actions of native oxyntomodulin are believed to be evenly split between the glucagon receptor (and, hence, increased hepatic glucose production) and GLP-1 receptor (and, hence, augmented glucose-dependent insulin secretion), the optimal ratio of receptor activation from the glucose-lowering perspective is yet to be determined.

The first human study of oxyntomodulin specifically in the context of DEP was published in 2017 [114]. This COSMOS study of individuals after an attack of acute pancreatitis showed that fasting levels of oxyntomodulin were significantly lower in those with PPDM than those with normoglycemia. The finding was consistent across all the statistical models, including the fully adjusted model accounting for sex, age, BMI, ethnicity, smoking, physical activity, etiology, time since first attack, severity, and recurrence of acute pancreatitis. At the same time, there was no significant difference between the groups in terms of fasting GLP-1 in any statistical model. Postprandial levels of oxyntomodulin were then investigated in a 2019 COSMOS study [115]. Oxyntomodulin was significantly lower in individuals with PPDM than in healthy volunteers, irrespective of sex, age, and body fat composition. Postprandial levels of GLP-1 were not significantly different between the groups. A 2020 COSMOS study compared the levels of oxyntomodulin between individuals with PPDM and those with type 2 diabetes [116]. Both fasting and postprandial levels of oxyntomodulin were significantly lower in the former, irrespective of sex, age, body composition, and β cell function. By contrast, both fasting and postprandial levels of GLP-1 were significantly higher in individuals with type 2 diabetes. A 2022 COSMOS study investigated factors affecting fasting levels of oxyntomodulin in individuals after an attack of acute pancreatitis [117]. It found that oxyntomodulin was significantly inversely associated with glycated hemoglobin (that explained 9% of the variance in oxyntomodulin) and directly associated with cholecystokinin (that explained 44% of the variance in oxyntomodulin). Given that cholecystokinin is a major exocrine pancreas secretagogue, the consistently low circulating levels of oxyntomodulin observed in individuals with PPDM may, in part, be indicative of exocrine pancreatic dysfunction. To date, several long-acting GLP-1/glucagon receptor co-agonists have been studied in individuals with type 2 diabetes but none has progressed to Phase III trials as they have not been able to reach the efficacy bar set high by GLP-1 receptor mono-agonists (and, more recently, GLP-1/GIP receptor co-agonists). Based on the findings presented above, it is argued that, among people with DEP, GLP-1/glucagon receptor co-agonism may have the highest therapeutic potential specifically in individuals with PPDM. Clinical trials will be needed to establish the efficacy and

safety of such agents in DEP, especially given the uncertain but widely known GLP-1 receptor agonist safety problem described above.

6 Conclusion

A large number of studies over the past 5 years or so has identified unique risk factors, natural history, and signatures of DEP [38, 118–120]. These recent advances set the stage for progress in pharmacological management of DEP in the decades to come. The present therapeutic armamentarium enables individualized treatment plans, in principle. However, the age-old dogma of insulin deficiency being the key underlying mechanism in all people with diabetes in the context of diseases of the exocrine pancreas needs to be abandoned to achieve this goal. One indicator of the current pharmacological management of DEP being suboptimal (or even harmful) and, hence, the need for the above-mentioned paradigm shift is a lower life expectancy in PPDM as compared with either type 1 or type 2 diabetes [121]. In future, not far away, personalized risk-benefit potential of a specific drug in people with DEP will need to consider the presence of comorbidities, and also life expectancy (in particular, in individuals with pancreatic cancer). Non-glycemic beneficial effects of some of the newer therapies (e.g., cardiovascular benefits with GLP-1 agonists and SGLT-2 inhibitors, renal and heart failure benefits of SGLT-2 inhibitors) also need to be considered as part of this holistic approach. Research focused specifically on DEP is evolving and new therapies will likely emerge and become part of an individualized treatment regimen in the future.

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References

1. Cho J, Petrov MS. Pancreatitis, pancreatic cancer, and their metabolic sequelae: projected burden to 2050. Clin Transl Gastroenterol. 2020;11:e00251.
2. Petrov MS, Basina M. DIAGNOSIS OF ENDOCRINE DISEASE: diagnosing and classifying diabetes in diseases of the exocrine pancreas. Eur J Endocrinol. 2021;184:R151–63.
3. The Diabetes Control and Complications Trial (DCCT). Design and methodologic considerations for the feasibility phase. The DCCT Research Group. Diabetes. 1986;35:530-45.
4. UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress and performance. Diabetologia. 1991;34:877-90.
5. Vonderau JS, Desai CS. Type 3c: understanding pancreatogenic diabetes. JAAPA. 2022;35:20–4.
6. Hart PA, Bellin MD, Andersen DK, et al. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. Lancet Gastroenterol Hepatol. 2016;1:226–37.
7. Rickels MR, Bellin M, Toledo FG, et al. Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: recommendations from PancreasFest 2012. Pancreatology. 2013;13:336–42.
8. Lohr JM, Dominguez-Munoz E, Rosendahl J, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United Eur Gastroenterol J. 2017;5:153–99.
9. Uc A, Andersen DK, Bellin MD, et al. Chronic pancreatitis in the 21st century—research challenges and opportunities: summary of a national institute of diabetes and digestive and kidney diseases workshop. Pancreas. 2016;45:1365–75.
10. Cui Y, Andersen DK. Pancreatogenic diabetes: special considerations for management. Pancreatology. 2011;11:279–94.
11. Shimizu K, Ito T, Irisawa A, et al. Evidence-based clinical practice guidelines for chronic pancreatitis 2021. J Gastroenterol. 2022;57:709–24.
12. Ramalho GX, Dytz MG. Diabetes of the exocrine pancreas related to hereditary pancreatitis, an update. Curr Diab Rep. 2020;20:16.
13. Moran A, Brunzell C, Cohen RC, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. Diabetes Care. 2010;33:2697–708.
14. Moran A, Pekow P, Grover P, et al. Insulin therapy to improve BMI in cystic fibrosis-related diabetes without fasting

hyperglycemia: results of the cystic fibrosis related diabetes therapy trial. Diabetes Care. 2009;32:1783–8.
15. Bellin MD. Pancreatogenic diabetes in children with recurrent acute and chronic pancreatitis: risks, screening, and treatment (mini-review). Front Pediatr. 2022;10:884668.
16. Bellin MD, Lowe M, Zimmerman MB, et al. Diabetes mellitus in children with acute recurrent and chronic pancreatitis: data from the international study group of pediatric pancreatitis: in search for a CuRE cohort. J Pediatr Gastroenterol Nutr. 2019;69:599–606.
17. Olesen SS, Toledo FG, Hart PA. The spectrum of diabetes in acute and chronic pancreatitis. Curr Opin Gastroenterol. 2022;38:509–15.
18. Price S, Cole D, Alcolado JC. Diabetes due to exocrine pancreatic disease–a review of patients attending a hospital-based diabetes clinic. QJM. 2010;103:759–63.
19. Wynne K, Devereaux B, Dornhorst A. Diabetes of the exocrine pancreas. J Gastroenterol Hepatol. 2019;34:346–54.
20. Viggers R, Jensen MH, Laursen HV, et al. Glucose-lowering therapy in patients with postpancreatitis diabetes mellitus: a nationwide population-based cohort study. Diabetes Care. 2021;44:2045–52.
21. Woodmansey C, McGovern AP, McCullough KA, et al. Incidence, demographics, and clinical characteristics of diabetes of the exocrine pancreas (type 3c): a retrospective cohort study. Diabetes Care. 2017;40:1486–93.
22. Santos R, Coleman HG, Cairnduff V, et al. Clinical prediction models for pancreatic cancer in general and at-risk populations: a systematic review. Am J Gastroenterol. 2023;118:26–40.
23. Wang Z, Lai ST, Xie L, et al. Metformin is associated with reduced risk of pancreatic cancer in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2014;106:19–26.
24. Singh S, Singh PP, Singh AG, et al. Anti-diabetic medications and risk of pancreatic cancer in patients with diabetes mellitus: a systematic review and meta-analysis. Am J Gastroenterol. 2013;108:510–9.
25. Li D, Yeung SC, Hassan MM, et al. Antidiabetic therapies affect risk of pancreatic cancer. Gastroenterology. 2009;137:482–8.
26. Cho J, Scragg R, Petrov MS. Postpancreatitis diabetes confers higher risk for pancreatic cancer than type 2 diabetes: results from a nationwide cancer registry. Diabetes Care. 2020;43:2106–12.
27. Shi YQ, Zhou XC, Du P, et al. Relationships are between metformin use and survival in pancreatic cancer patients concurrent with diabetes: a systematic review and meta-analysis. Medicine (Baltimore). 2020;99:e21687.
28. Reni M, Dugnani E, Cereda S, et al. (Ir)relevance of metformin treatment in patients with metastatic pancreatic cancer: an open-label, randomized phase II trial. Clin Cancer Res. 2016;22:1076–85.
29. Kordes S, Pollak MN, Zwinderman AH, et al. Metformin in patients with advanced pancreatic cancer: a double-blind, randomised, placebo-controlled phase 2 trial. Lancet Oncol. 2015;16:839–47.
30. Cho J, Scragg R, Pandol SJ, et al. Antidiabetic medications and mortality risk in individuals with pancreatic cancer-related diabetes and postpancreatitis diabetes: a nationwide cohort study. Diabetes Care. 2019;42:1675–83.
31. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393–403.
32. Ito T, Otsuki M, Itoi T, et al. Pancreatic diabetes in a follow-up survey of chronic pancreatitis in Japan. J Gastroenterol. 2007;42:291–7.
33. Wang W, Guo Y, Liao Z, et al. Occurrence of and risk factors for diabetes mellitus in Chinese patients with chronic pancreatitis. Pancreas. 2011;40:206–12.
34. Bharmal SH, Cho J, Alarcon Ramos GC, et al. Trajectories of glycaemia following acute pancreatitis: a prospective longitudinal cohort study with 24 months follow-up. J Gastroenterol. 2020;55:775–88.
35. Das SL, Singh PP, Phillips AR, et al. Newly diagnosed diabetes mellitus after acute pancreatitis: a systematic review and meta-analysis. Gut. 2014;63:818–31.
36. Zhi M, Zhu X, Lugea A, et al. Incidence of new onset diabetes mellitus secondary to acute pancreatitis: a systematic review and meta-analysis. Front Physiol. 2019;10:637.
37. Soo DH, Pendharkar SA, Jivanji CJ, et al. Derivation and validation of the prediabetes self-assessment screening score after acute pancreatitis (PERSEUS). Dig Liver Dis. 2017;49:1146–54.
38. Jeon C, Hart PA, Li L, et al. Development of a clinical prediction model for diabetes in chronic pancreatitis: the PREDICT3c Study. Diabetes Care. 2023;46:46–55.
39. Cho J, Scragg R, Petrov MS. Risk of mortality and hospitalization after post-pancreatitis diabetes mellitus vs type 2 diabetes mellitus: a population-based matched cohort study. Am J Gastroenterol. 2019;114:804–12.
40. Zhu X, Liu D, Wei Q, et al. New-onset diabetes mellitus after chronic pancreatitis diagnosis: a systematic review and meta-analysis. Pancreas. 2019;48:868–75.
41. Raue G, Keim V. Secondary diabetes in chronic pancreatitis. Z Gastroenterol. 1999;1:4–9.
42. Lankisch PG. Conservative treatment of chronic pancreatitis. Digestion. 1987;37(Suppl 1):47–55.
43. Valdez-Hernandez P, Perez-Diaz I, Soriano-Rios A, et al. Pancreatogenic diabetes, 2 onset forms and lack of metabolic syndrome components differentiate it from type 2 diabetes. Pancreas. 2021;50:1376–81.
44. Lee N, Park SJ, Kang D, et al. Characteristics and clinical course of diabetes of the exocrine pancreas: a nationwide population-based cohort study. Diabetes Care. 2022;45:1141–50.
45. Lanzinger S, Karges W, Merger S, et al. Comparing diabetes due to diseases of the exocrine pancreas to type 1 and type 2 diabetes using propensity score matching. Pancreatology. 2020;20:860–6.
46. Olesen SS, Svane HML, Nicolaisen SK, et al. Clinical and biochemical characteristics of postpancreatitis diabetes mellitus: a cross-sectional study from the Danish nationwide DD2 cohort. J Diabetes. 2021;13:960–74.
47. Dytz MG, Marcelino PA, de Castro SO, et al. Clinical aspects of pancreatogenic diabetes secondary to hereditary pancreatitis. Diabetol Metab Syndr. 2017;9:4.
48. Liu QC, Zhuang ZH, Zeng K, et al. Prevalence of pancreatic diabetes in patients carrying mutations or polymorphisms of the PRSS1 gene in the Han population. Diabetes Technol Ther. 2009;11:799–804.
49. Struyvenberg MR, Fong ZV, Martin CR, et al. Impact of treatments on diabetic control and gastrointestinal symptoms after total pancreatectomy. Pancreas. 2017;46:1188–95.
50. van Veldhuisen CL, Latenstein AE, Blauw H, et al. Bihormonal artificial pancreas with closed-loop glucose control vs current diabetes care after total pancreatectomy: a randomized clinical trial. JAMA Surg. 2022;157:950–7.
51. Lee DY, Yu JH, Park S, et al. The influence of diabetes and antidiabetic medications on the risk of pancreatic cancer: a nationwide population-based study in Korea. Sci Rep. 2018;8:9719.
52. Lu Y, Garcia Rodriguez LA, Malgerud L, et al. New-onset type 2 diabetes, elevated HbA1c, anti-diabetic medications, and risk of pancreatic cancer. Br J Cancer. 2015;113:1607–14.

53. Shen B, Li Y, Sheng CS, et al. Association between age at diabetes onset or diabetes duration and subsequent risk of pancreatic cancer: results from a longitudinal cohort and mendelian randomization study. Lancet Reg Health West Pac. 2023;30:100596.
54. Colmers IN, Bowker SL, Tjosvold LA, et al. Insulin use and cancer risk in patients with type 2 diabetes: a systematic review and meta-analysis of observational studies. Diabetes Metab. 2012;38:485–506.
55. Li D, Tang H, Hassan MM, et al. Diabetes and risk of pancreatic cancer: a pooled analysis of three large case-control studies. Cancer Causes Control. 2011;22:189–97.
56. Bosetti C, Rosato V, Li D, et al. Diabetes, antidiabetic medications, and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case–Control Consortium. Ann Oncol. 2014;25:2065–72.
57. Cho J, Scragg R, Petrov MS. Use of insulin and the risk of progression of pancreatitis: a population-based cohort study. Clin Pharmacol Ther. 2020;107:580–7.
58. Olesen SS, Viggers R, Drewes AM, et al. Risk of major adverse cardiovascular events, severe hypoglycemia, and all-cause mortality in postpancreatitis diabetes mellitus versus type 2 diabetes: a nationwide population-based cohort study. Diabetes Care. 2022;45:1326–34.
59. Duggan SN, Smyth ND, Murphy A, et al. High prevalence of osteoporosis in patients with chronic pancreatitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2014;12:219–28.
60. Zhou X, You S. Rosiglitazone inhibits hepatic insulin resistance induced by chronic pancreatitis and IKK-beta/NF-kappaB expression in liver. Pancreas. 2014;43:1291–8.
61. Pendharkar SA, Asrani VM, Xiao AY, et al. Relationship between pancreatic hormones and glucose metabolism: a cross-sectional study in patients after acute pancreatitis. Am J Physiol Gastrointest Liver Physiol. 2016;311:G50–8.
62. Permert J, Adrian TE, Jacobsson P, et al. Is profound peripheral insulin resistance in patients with pancreatic cancer caused by a tumor-associated factor? Am J Surg. 1993;165:61–6.
63. Brunicardi FC, Chaiken RL, Ryan AS, et al. Pancreatic polypeptide administration improves abnormal glucose metabolism in patients with chronic pancreatitis. J Clin Endocrinol Metab. 1996;81:3566–72.
64. Ballmann M, Hubert D, Assael BM, et al. Repaglinide versus insulin for newly diagnosed diabetes in patients with cystic fibrosis: a multicentre, open-label, randomised trial. Lancet Diabetes Endocrinol. 2018;6:114–21.
65. Nauck MA, Heimesaat MM, Orskov C, et al. Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. J Clin Invest. 1993;91:301–7.
66. Knop FK, Vilsboll T, Hojberg PV, et al. The insulinotropic effect of GIP is impaired in patients with chronic pancreatitis and secondary diabetes mellitus as compared to patients with chronic pancreatitis and normal glucose tolerance. Regul Pept. 2007;144:123–30.
67. Vilsboll T, Knop FK, Krarup T, et al. The pathophysiology of diabetes involves a defective amplification of the late-phase insulin response to glucose by glucose-dependent insulinotropic polypeptide-regardless of etiology and phenotype. J Clin Endocrinol Metab. 2003;88:4897–903.
68. Hedetoft C, Sheikh SP, Larsen S, et al. Effect of glucagon-like peptide 1(7–36)amide in insulin-treated patients with diabetes mellitus secondary to chronic pancreatitis. Pancreas. 2000;20:25–31.
69. Elashoff M, Matveyenko AV, Gier B, et al. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterology. 2011;141:150–6.
70. Forsmark CE. Incretins, diabetes, pancreatitis and pancreatic cancer: what the GI specialist needs to know. Pancreatology. 2016;16:10–3.
71. Storgaard H, Cold F, Gluud LL, et al. Glucagon-like peptide-1 receptor agonists and risk of acute pancreatitis in patients with type 2 diabetes. Diabetes Obes Metab. 2017;19:906–8.
72. Cao C, Yang S, Zhou Z. GLP-1 receptor agonists and pancreatic safety concerns in type 2 diabetic patients: data from cardiovascular outcome trials. Endocrine. 2020;68:518–25.
73. Abd El Aziz M, Cahyadi O, Meier JJ, et al. Incretin-based glucose-lowering medications and the risk of acute pancreatitis and malignancies: a meta-analysis based on cardiovascular outcomes trials. Diabetes Obes Metab. 2020;22:699–704.
74. Singh AK, Gangopadhyay KK, Singh R. Risk of acute pancreatitis with incretin-based therapy: a systematic review and updated meta-analysis of cardiovascular outcomes trials. Expert Rev Clin Pharmacol. 2020;13:461–8.
75. Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs–FDA and EMA assessment. N Engl J Med. 2014;370:794–7.
76. Bang UC, Benfield T, Hyldstrup L, et al. Mortality, cancer, and comorbidities associated with chronic pancreatitis: a Danish nationwide matched-cohort study. Gastroenterology. 2014;146:989–94.
77. Kirkegard J, Cronin-Fenton D, Heide-Jorgensen U, et al. Acute pancreatitis and pancreatic cancer risk: a nationwide matched-cohort study in Denmark. Gastroenterology. 2018;154:1729–36.
78. Munigala S, Almaskeen S, Subramaniam DS, et al. Acute pancreatitis recurrences augment long-term pancreatic cancer risk. Am J Gastroenterol. 2023;118:727–37.
79. Rosenstock J, Wysham C, Frias JP, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. Lancet. 2021;398:143–55.
80. Knop FK, Vilsboll T, Larsen S, et al. Increased postprandial responses of GLP-1 and GIP in patients with chronic pancreatitis and steatorrhea following pancreatic enzyme substitution. Am J Physiol Endocrinol Metab. 2007;292:E324–30.
81. Hornum M, Pedersen JF, Larsen S, et al. Increased postprandial response of glucagon-like peptide-2 in patients with chronic pancreatitis and pancreatic exocrine insufficiency. Pancreatology. 2010;10:201–7.
82. Ebert R, Creutzfeldt W. Reversal of impaired GIP and insulin secretion in patients with pancreatogenic steatorrhea following enzyme substitution. Diabetologia. 1980;19:198–204.
83. Knop FK, Vilsboll T, Hojberg PV, et al. Reduced incretin effect in type 2 diabetes: cause or consequence of the diabetic state? Diabetes. 2007;56:1951–9.
84. Kuo P, Stevens JE, Russo A, et al. Gastric emptying, incretin hormone secretion, and postprandial glycemia in cystic fibrosis—effects of pancreatic enzyme supplementation. J Clin Endocrinol Metab. 2011;96:E851–5.
85. Perano SJ, Couper JJ, Horowitz M, et al. Pancreatic enzyme supplementation improves the incretin hormone response and attenuates postprandial glycemia in adolescents with cystic fibrosis: a randomized crossover trial. J Clin Endocrinol Metab. 2014;99:2486–93.
86. Sattar N, Lee MM, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol. 2021;9:653–62.
87. Jamil S, Zainab A, Arora A, et al. Efficacy and safety of sodium glucose cotransporter-2 (SGLT2) inhibitors in patients with

diabetes and chronic kidney disease (CKD): a meta-analysis of randomized control trials. Cureus. 2022;14:e31898.
88. Hart PA, Andersen DK, Petrov MS, et al. Distinguishing diabetes secondary to pancreatic diseases from type 2 diabetes mellitus. Curr Opin Gastroenterol. 2021;37:520–5.
89. Petrov MS. Panorama of mediators in postpancreatitis diabetes mellitus. Curr Opin Gastroenterol. 2020;36:443–51.
90. Wei Q, Qi L, Lin H, et al. Pathological mechanisms in diabetes of the exocrine pancreas: what's known and what's to know. Front Physiol. 2020;11:570276.
91. Gillies NA, Pendharkar SA, Singh RG, et al. Lipid metabolism in patients with chronic hyperglycemia after an episode of acute pancreatitis. Diabetes Metab Syndr. 2017;11(Suppl 1):233–41.
92. Bharmal SH, Pendharkar SA, Singh RG, et al. Associations between ketone bodies and fasting plasma glucose in individuals with post-pancreatitis prediabetes. Arch Physiol Biochem. 2020;126:308–19.
93. Jimenez-Luna C, Martin-Blazquez A, Dieguez-Castillo C, et al. Novel biomarkers to distinguish between type 3c and type 2 diabetes mellitus by untargeted metabolomics. Metabolites. 2020;10:423.
94. Olesen SS, Poulsen JL, Novovic S, et al. Multiple risk factors for diabetes mellitus in patients with chronic pancreatitis: a multicentre study of 1117 cases. United Eur Gastroenterol J. 2020;8:453–61.
95. Zhang J, Lv Y, Hou J, et al. Machine learning for post-acute pancreatitis diabetes mellitus prediction and personalized treatment recommendations. Sci Rep. 2023;13:4857.
96. Thiruvengadam NR, Schaubel DE, Forde K, et al. Association of statin usage and the development of diabetes mellitus after acute pancreatitis. Clin Gastroenterol Hepatol. 2023;21:1214–22.
97. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010;375:735–42.
98. Liu Y, Bharmal SH, Kimita W, et al. Effect of acute ketosis on lipid profile in prediabetes: findings from a cross-over randomized controlled trial. Cardiovasc Diabetol. 2022;21:138.
99. Bharmal SH, Cho J, Alarcon Ramos GC, et al. Acute nutritional ketosis and its implications for plasma glucose and glucoregulatory peptides in adults with prediabetes: a crossover placebo-controlled randomized trial. J Nutr. 2021;151:921–9.
100. Petrov MS. Fatty change of the pancreas: the Pandora's box of pancreatology. Lancet Gastroenterol Hepatol. 2023;8:671–82.
101. Kloppel G, Bommer G, Commandeur G, et al. The endocrine pancreas in chronic pancreatitis. Immunocytochemical and ultrastructural studies. Virchows Arch A Pathol Anat Histol. 1978;377:157–74.
102. Adrian TE, Bloom SR, Bryant MG, et al. Distribution and release of human pancreatic polypeptide. Gut. 1976;17:940–4.
103. Koch MB, Go VL, DiMagno EP. Can plasma human pancreatic polypeptide be used to detect diseases of the exocrine pancreas? Mayo Clin Proc. 1985;60:259–65.
104. Yamamura T, Mori K, Tatsumi M, et al. Availability of plasma pancreatic polypeptide measurement in diagnosis of chronic pancreatitis. Scand J Gastroenterol. 1981;16:757–61.
105. Lamers CB, Diemel CM, Jansen JB. Comparative study of plasma pancreatic polypeptide responses to food, secretin, and bombesin in normal subjects and in patients with chronic pancreatitis. Dig Dis Sci. 1984;29:102–8.
106. Qi L, Wei Q, Ni M, et al. Pancreatic and gut hormone responses to mixed meal test in post-chronic pancreatitis diabetes mellitus. Diabetes Metab. 2022;48:101316.
107. Hart PA, Kudva YC, Yadav D, et al. A reduced pancreatic polypeptide response is associated with new onset pancreatogenic diabetes versus type 2 diabetes. J Clin Endocrinol Metab. 2023;108:e120–8.
108. Hart PA, Baichoo E, Bi Y, et al. Pancreatic polypeptide response to a mixed meal is blunted in pancreatic head cancer associated with diabetes mellitus. Pancreatology. 2015;15:162–6.
109. Seymour NE, Brunicardi FC, Chaiken RL, et al. Reversal of abnormal glucose production after pancreatic resection by pancreatic polypeptide administration in man. Surgery. 1988;104:119–29.
110. Tan TM, Field BC, Minnion JS, et al. Pharmacokinetics, adverse effects and tolerability of a novel analogue of human pancreatic polypeptide, PP 1420. Br J Clin Pharmacol. 2012;73:232–9.
111. Waser B, Blank A, Karamitopoulou E, et al. Glucagon-like-peptide-1 receptor expression in normal and diseased human thyroid and pancreas. Mod Pathol. 2015;28:391–402.
112. Kirk RK, Pyke C, von Herrath MG, et al. Immunohistochemical assessment of glucagon-like peptide 1 receptor (GLP-1R) expression in the pancreas of patients with type 2 diabetes. Diabetes Obes Metab. 2017;19:705–12.
113. Shankar SS, Shankar RR, Mixson LA, et al. Native oxyntomodulin has significant glucoregulatory effects independent of weight loss in obese humans with and without type 2 diabetes. Diabetes. 2018;67:1105–12.
114. Pendharkar SA, Asrani VM, Murphy R, et al. The role of gut-brain axis in regulating glucose metabolism after acute pancreatitis. Clin Transl Gastroenterol. 2017;8:210.
115. Pendharkar SA, Singh RG, Cervantes A, et al. Gut hormone responses to mixed meal test in new-onset prediabetes/diabetes after acute pancreatitis. Horm Metab Res. 2019;51:191–9.
116. Bharmal SH, Cho J, Stuart CE, et al. Oxyntomodulin may distinguish new-onset diabetes after acute pancreatitis from type 2 diabetes. Clin Transl Gastroenterol. 2020;11:00132.
117. Bharmal SH, Ko J, Kimita W, et al. Factors affecting the circulating levels of oxyntomodulin in health and after acute pancreatitis. Pancreas. 2022;51:774–83.
118. Goodarzi MO, Petrov MS, Andersen DK, et al. Diabetes in chronic pancreatitis: risk factors and natural history. Curr Opin Gastroenterol. 2021;37:526–31.
119. Li G, Sun J, Zhang J, et al. Identification of inflammation-related biomarkers in diabetes of the exocrine pancreas with the use of weighted gene co-expression network analysis. Front Endocrinol (Lausanne). 2022;13:839865.
120. Gal E, Dolensek J, Stozer A, et al. Mechanisms of post-pancreatitis diabetes mellitus and cystic fibrosis-related diabetes: a review of preclinical studies. Front Endocrinol (Lausanne). 2021;12:715043.
121. Cho J, Pandol SJ, Petrov MS. Risk of cause-specific death, its sex and age differences, and life expectancy in post-pancreatitis diabetes mellitus. Acta Diabetol. 2021;58:797–807.