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REVIEW IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Metabolic Sequelae: The Pancreatitis Zeitgeist of the 21st Century

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Holistic management of pancreatitis means that gastroenterologists in the 21st Century should think beyond improving in-hospital outcomes of pancreatitis alone. In particular, there is considerable room for optimizing the management of new-onset diabetes, exocrine pancreatic insufficiency, and other metabolic sequelae of pancreatitis. The present article provides state-of-the-art information on classification, terminology, and burden of the common sequelae of pancreatitis. A high-risk group of patients with pancreatitis is identified, which is positioned to benefit the most from the metabolic sequelae surveillance program introduced in this article. The program involves continuous follow-up after pancreatitis diagnosis, with the focus on early identification of new-onset diabetes after pancreatitis and exocrine pancreatic insufficiency. The metabolic sequelae surveillance program is scalable and has the potential to reduce the burden of pancreatitis through tertiary prevention in the decades to come.

Keywords: Acute Pancreatitis; Chronic Pancreatitis; Surveillance Program; New-Onset Diabetes; Exocrine Pancreatic Insufficiency; Osteoporosis; Sarcopenia; Dyslipidemia.

Pancreatitis as a disease entity was established in the second half of the 19th Century and there have been several major advances in knowledge. These advances, each corresponding to a pancreatitis zeitgeist (ie, the intellectual climate of an era that facilitates scientific progress), have led to where the disease stands in the first quarter of the 21st Century. With a global incidence of ∼35 cases per 100,000 person-years for acute pancreatitis and ∼10 cases per 100,000 person-years for chronic pancreatitis, acute and chronic pancreatitis are among the most common diseases in routine gastroenterology practice worldwide.[1,2] The improved management of pancreatitis over the past few decades, including the growing availability of high-resolution imaging, incremental innovations in endoscopy, and gradual abandonment of open surgery, has contributed to the current lowest in-hospital mortality from pancreatitis on record.[1,3] However, the mortality trough has likely been reached because there is no specific treatment on the horizon that would realistically be able to target the pathogenesis of pancreatitis in humans in the foreseeable future.[4,5] Although a further decrease in deaths from pancreatitis is not expected, the overall burden of pancreatitis can still be meaningfully reduced if the focus of pancreatitis management is expanded beyond the classical secondary prevention (ie, application of effective interventions early in the course of disease with a view to reducing mortality during hospitalization). In particular, tertiary prevention of pancreatitis – aimed at minimizing the development (or effects) of its sequelae after hospital discharge – is poised to become a cornerstone of pancreatitis management in the decades to come.[6] The unmet need for gastroenterologists to be aware of pancreatitis conferring long-term risks of new-onset diabetes, exocrine insufficiency, and other metabolic sequelae formed the basis for the present article.

New-Onset Diabetes After Pancreatitis

Terminology and Classification

New-onset diabetes after pancreatitis (NODAP) is defined as diabetes developed in a previously nondiabetic patient with a history of acute pancreatitis or chronic pancreatitis. NODAP is a unified umbrella term and, hence, covers not only diabetes after common pancreatitis etiologies but also diabetes secondary to relatively uncommon entities, such as hereditary pancreatitis, autoimmune pancreatitis, and fibrocalculous pancreatopathy (also referred to as tropical calcific pancreatitis).[7] Diabetes secondary to disconnected pancreatic duct syndrome (that sometimes develops during acute necrotizing pancreatitis) is covered by the term NODAP too.[8]

Identification of NODAP involves the following principal steps (Figure 1). First, the nondiabetic status of a patient with a history of pancreatitis should be confirmed based on the absence of diabetes diagnosis (of any recognized type) in medical records or no recorded changes of lifestyle and use of glucose-lowering medications (for the purpose of treating diabetes) before pancreatitis diagnosis.[7] Patient

Abbreviations used in this paper: **BMI, body mass index; BMD, bone mineral density; EPD, exocrine pancreatic dysfunction; EPI, exocrine pancreatic insufficiency; HR, hazard ratio; MSSP, metabolic sequelae surveillance program; NODAP, new-onset diabetes after pancreatitis; NOPAP, new-onset prediabetes after pancreatitis; OR, odds ratio; PPDM, postpancreatitis diabetes mellitus.**

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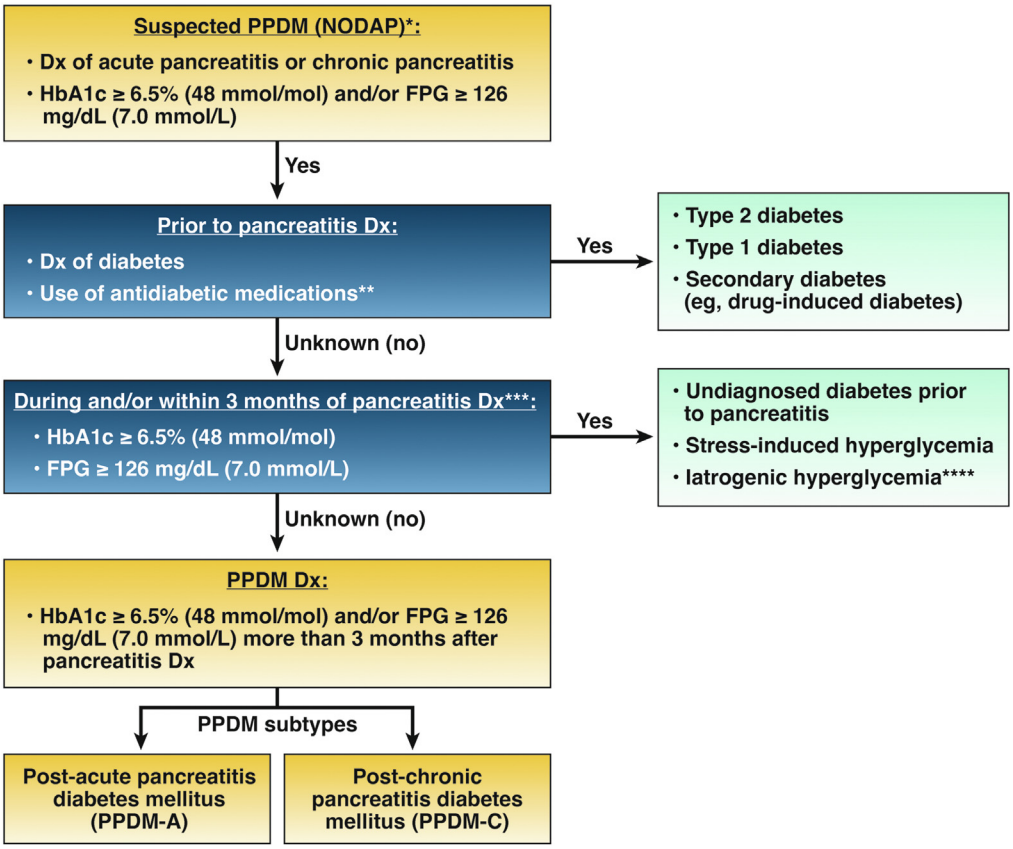

Figure 1. Operational guideline for the identification of NODAP and PPDM. *In the context of the present guideline, if a patient with diabetes with no proof of pre-existing diabetes mellitus does not have glycated hemoglobin and/or fasting plasma glucose data available (or these values are inconclusive due to, for example, chronic disorders interfering with the accuracy of measurements) before and/or within 3 months of pancreatitis Dx, the recommended term is PPDM. If a patient with diabetes with no proof of pre-existing diabetes mellitus has glycated hemoglobin and/or fasting plasma glucose data available before and/or within 3 months of pancreatitis Dx, the recommended term is NODAP. In other words, the absence of laboratory evidence of diabetes before pancreatitis is equated to a normal result in the case of PPDM whereas the presence of a normal laboratory result is required in the case of NODAP. Although NODAP represents the "pure" population of patients with incident diabetes secondary to pancreatitis, PPDM covers a broader population of patients with diabetes and allows for a degree of "contamination" (because sometimes there can be not enough data available to rule out pre-existing undiagnosed diabetes or other scenarios when prevalent cases of diabetes cannot be ruled out with certainty). These stipulations for the use of the term NODAP are generally met in prospective studies whereas the term PPDM may often be appropriately used in retrospective studies. **Use of antidiabetic medications for the purpose of managing conditions other than diabetes (eg, cardiovascular diseases, chronic kidney disease, or polycystic ovary syndrome) before pancreatitis Dx does not preclude the possibility of having PPDM (NODAP). ***Glycated hemoglobin 6.5% (48 mmol/mol) during hospitalization for pancreatitis or shortly thereafter signifies undiagnosed diabetes before pancreatitis and, therefore, rules out NODAP Dx. Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L) during hospitalization for pancreatitis in a patient without pre-existing diabetes mellitus signifies stress-induced hyperglycemia or iatrogenic hyperglycemia (and, therefore, rules out NODAP Dx), unless it persists beyond 3 months after pancreatitis Dx or NODAP Dx is established based on meeting the glycated hemoglobin criterion beyond 3 months after pancreatitis Dx (Table 1). ****Iatrogenic hyperglycemia develops in a patient without pre-existing diabetes (diagnosed or undiagnosed) as a result of in-hospital management of pancreatitis (eg, intravenous infusion of dextrose or use of parenteral nutrition). Dx, diagnosis; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; NODAP, new-onset diabetes after pancreatitis; PPDM, postpancreatitis diabetes mellitus.

self-report alone is not sufficient. It is acknowledged that occasionally patients who had symptoms suggestive of pancreatitis for years later present with diabetes at the time of first formal chronic pancreatitis diagnosis. On the other hand, it is known that sometimes chronic pancreatitis can be painless (or even asymptomatic).[9] Therefore, the operational guideline is pragmatic and based on the date of pancreatitis diagnosis in relation to the date of diabetes diagnosis. In particular, symptoms of abnormal exocrine function of the pancreas (without a formal diagnosis of chronic pancreatitis) in a patient who was later diagnosed with new-onset diabetes is not sufficient to meet the NODAP criteria. Second, biochemical diagnostic criteria should be used to rule out undiagnosed pre-existing diabetes.[10] This is important because undiagnosed pre-existing diabetes contributes approximately one third to the prevalence of diabetes in patients hospitalized for acute pancreatitis (determined based on glycated hemoglobin within 72 hours of hospitalization).[11] Fasting (or random) plasma glucose during hospitalization for pancreatitis should not be used

for ruling out pre-existing diabetes because of a high frequency of transient stress-induced hyperglycemia and iatrogenic hyperglycemia (after intravenous glucose infusion or administration of parenteral nutrition) in this population.[12–14] Nevertheless, hyperglycemia first identified during hospitalization for pancreatitis may persist long after hospital discharge and, therefore, herald NODAP. The diagnosis of NODAP is established no earlier than 3 months after diagnosis of pancreatitis based on the thresholds for glycated hemoglobin and/or fasting plasma glucose advocated by the American Diabetes Association (Table 1).[5] The corresponding presequela – new-onset prediabetes after pancreatitis (Figure 2) – is also diagnosed based on the American Diabetes Association thresholds (Table 1).[5] As an operational means of defining the most uniform group of people, diabetes diagnosed within 3 months after pancreatitis rules out the diagnosis of NODAP. This is because levels of glycated hemoglobin reflect average plasma glucose over the preceding 2–3 months and because disregarding the 3-month lag period leads to a markedly inflated risk of diabetes (adjusted hazard ratios 5.9 and 2.5 within and beyond 3 months after pancreatitis, respectively).[5,15] This guideline (Figure 1) has been used in numerous independent original studies from various regions of the world and has consistently met the logical expectations based on pathophysiology (eg, diabetes secondary to chronic pancreatitis requires more insulin than type 2 diabetes, diabetes secondary to chronic pancreatitis has more comorbidities as well as requires more pancreatic enzyme replacement therapy in comparison with diabetes secondary to acute pancreatitis, and higher frequency of hypoglycemia in diabetes secondary to pancreatitis than type 2 diabetes).[16–20] The use of the criteria outlined in the guideline (Figure 1) has also facilitated a meaningful comparison of findings from different centers,[6,21] which is essential for accelerating progress in this highly multidisciplinary field.

Although not every patient with increased blood glucose in the setting of pancreatitis has NODAP, a given individual with diabetes cannot have simultaneously more than one diagnosis of a specific type of diabetes.[7] This is analogous to increased blood pressure; the same patient cannot simultaneously have both primary (essential) hypertension and secondary hypertension (due to a specific cause such as pheochromocytoma, thyroid disease, or Cushing syndrome). Although type 2 diabetes is the most common type of diabetes and primary hypertension is the most common type of arterial hypertension, both are basically diagnoses of exclusion.[7] It follows that healthcare professionals should be aware of secondary diseases and, in particular, identify a specific cause of diabetes (NODAP in the case of gastroenterologists).[21] Furthermore, taking into account that individuals with secondary hypertension are often initially diagnosed with primary hypertension, it is possible that patients with NODAP are initially labeled as having type 2 diabetes (eg, when a history of pancreatitis in the individual with diabetes is not considered or missed).[22,23] Another caveat gastroenterologists should be aware of is that the term "type 3c diabetes," sometimes used in the past, is a misnomer and its use has never been ratified by any (inter) national professional body in the field of diabetology.[7] The reasons for the confusion were described in detail elsewhere and the use of this term is discouraged.[7] The term "diabetes of the exocrine pancreas" is a modern

Table 1. Diagnostic Criteria for the Main Metabolic Sequelae and Presequelae of Pancreatitis

	NODAP[a]	EPI[b]	Osteoporosis[c]
Sequelae	Glycated hemoglobin ≥6.5% (48 mmol/mol) Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L)	Coefficient of fat absorption <93%	Bone mineral density T score <−2.5
	NOPAP	**EPD**	**Osteopenia**
Presequelae	Glycated hemoglobin 5.7–6.4% (39–47 mmol/mol) Fasting plasma glucose 100–125 mg/dL (5.6–6.9 mmol/L)	Fecal elastase <200 μg/g	Bone mineral density T score between −1 and −2.5

[a]According to the guideline (Figure 1), establishing the Dx of NODAP (and by extension NOPAP) during and/or within 3 mo of pancreatitis Dx is not recommended. This does not rule out the possibility of initially identifying an abnormal level of fasting plasma glucose during and/or within 3 mo of pancreatitis Dx that subsequently forms the basis for diagnosing NODAP or NOPAP. Meeting the diagnostic criteria for NODAP or NOPAP requires 2 abnormal test results on simultaneous or consecutive testing (when there is no unequivocal hyperglycemia). Both glycated hemoglobin and fasting plasma glucose should be measured on a fresh, never frozen, sample. Glycated hemoglobin should be measured using a method certified by the National Glycohaemoglobin Standardization Program and standardized to the Diabetes Control and Complications Trial reference assay. Point-of-care devices should not be used for diagnosing NODAP or NOPAP. Fasting plasma glucose should be measured after no calorie intake for at least 8 h.
[b]Patients who meet the criteria for both EPI and EPD should be labeled as EPI only. Fecal elastase should not be measured in liquid stool because of the high risk of a false-negative result.
[c]Fragility fractures are deemed to represent underlying osteoporosis, regardless of bone mineral density T score.
EPD, exocrine pancreatic dysfunction; EPI, exocrine pancreatic insufficiency; NODAP, new-onset diabetes after pancreatitis; NOPAP, new-onset prediabetes after pancreatitis.

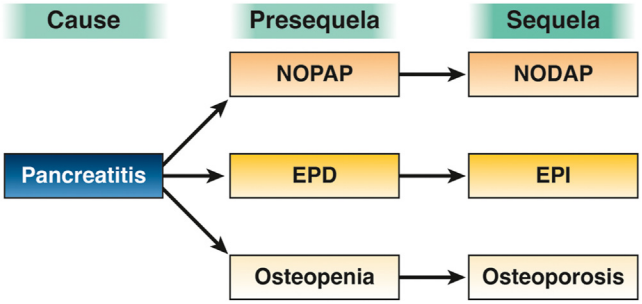

Figure 2. Main metabolic presequelae and sequelae of pancreatitis. Presequelae are precursors of sequelae. Once the criteria for a metabolic sequela have been met (Table 1), the patient with pancreatitis should not be labeled as having the corresponding presequela. EPD, exocrine pancreatic dysfunction; EPI, exocrine pancreatic insufficiency; NODAP, new-onset diabetes after pancreatitis; NOPAP, new-onset prediabetes after pancreatitis.

recommended blanket term for diabetes in the setting of diseases of the exocrine pancreas.[7] The term "post-pancreatitis diabetes mellitus" (PPDM) is adopted to describe a subtype of "diabetes of the exocrine pancreas" that encompasses patients with pancreatitis in whom establishing pre-existing diabetes mellitus is unclear (eg, incomplete laboratory data to evaluate the biochemical diagnostic criteria) and, therefore, the absence of proof of diabetes before pancreatitis is taken to mean that the diabetes is incident (by contrast, NODAP requires the presence of proof of not fulfilling the biochemical diagnostic criteria for diabetes mellitus before pancreatitis).[21] This scenario is common in retrospective studies, in particular, population-based investigations that use large administrative databases.[17,20,22] PPDM is subdivided into PPDM-A and PPDM-C when acute pancreatitis and chronic pancreatitis, respectively, underlie the diabetes (Figure 1).

Although this dichotomy is useful for operationalizing the guideline in the clinic and research setting, limitations of using categorical variables as proxies for continuous phenomena are appreciated. From the pathogenetic point of view alone, PPDM is best seen as a continuous spectrum: diabetes secondary to first attack of non-necrotizing acute pancreatitis lies at one end of the spectrum whereas diabetes secondary to end-stage chronic pancreatitis lies at the other end.[21] The primary driving forces are grossly different – overwhelming insulin resistance (and the resulting compensatory hyperinsulinemia) in the case of the former and critical loss of β cells in the case of the latter.[24–26] Hence, the pharmacologic management of the 2 subtypes of PPDM is markedly different.[27,28] At the same time, the key drivers of new-onset diabetes in less polar cases of pancreatitis (eg, diabetes secondary to recurrent acute pancreatitis or early chronic pancreatitis) are not as clear cut. They typically include various degrees of impairment in both insulin sensitivity and β-cell function.[21,29] The core pathologic signatures of this change in insulin traits are sustained low-grade inflammation, deranged lipid metabolism, and dysfunction of the pancreas-gut-brain axis.[30–34]

Burden of Sequela

The high frequency of PPDM-C has long been appreciated.[26] A 2019 meta-analysis aggregated data from 15 cross-sectional and retrospective cohort studies published between 1981 and 2018.[35] The study found that the pooled incidence of PPDM-C was 30%. Furthermore, there was the following relationship between incidence of PPDM and time since chronic pancreatitis diagnosis: 15% within 3 years after chronic pancreatitis, 31% in 3–5 years after chronic pancreatitis, and 33% in more than 5 years after chronic pancreatitis.[35] A 2019 population-based study from New Zealand (as part of the COSMOS program) found that, in comparison with type 2 diabetes, PPDM-C was associated with significantly higher all-cause mortality (adjusted hazard ratio [HR], 1.3).[36] This was independently confirmed in a 2022 population-based study from Denmark (adjusted HR, 1.5; Figure 3) and a 2022 population-based study from South Korea (adjusted odds ratio [OR], 1.4).[17,37] Furthermore, the study from Denmark found that PPDM-C, as compared with type 2 diabetes, was associated with a significantly higher risk of severe hypoglycemia (adjusted HR, 5.3).[37] An increased risk of hypoglycemia (adjusted OR, 1.9) in PPDM-C vs type 2 diabetes was also reported in the previously mentioned study from South Korea.[17] In addition, that study showed that PPDM-C influenced the development of microvascular complications – diabetic neuropathy, nephropathy, and retinopathy – with up to 1.5 times higher risks in comparison with type 2 diabetes.[17] Also, PPDM-C was associated with a significantly higher risk of developing psychiatric disorders (adjusted HR, 3.0) than chronic pancreatitis without diabetes, with the cumulative incidence of these disorders in patients with PPDM-C being 9.2%.[38] A 2021 population-based COSMOS study investigated cause-specific mortality and observed much higher cancer mortality, but not vascular or nonvascular noncancer mortality, in PPDM-C.[39] The analysis of site-specific cancer mortality found significantly higher risks of

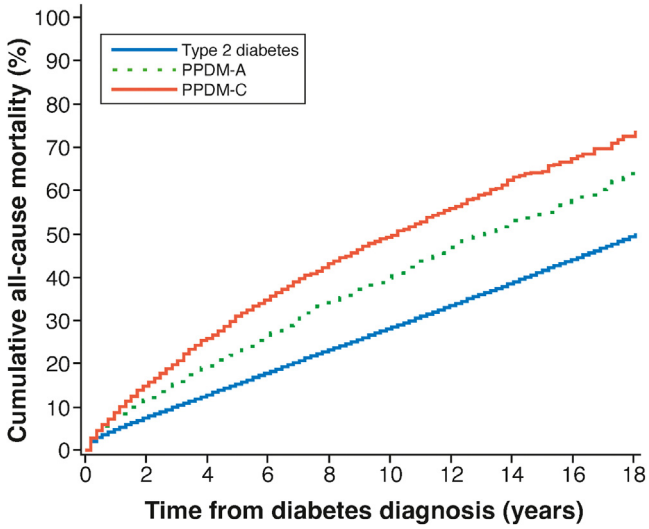

Figure 3. All-cause mortality in the subtypes of PPDM as compared with type 2 diabetes mellitus. Data are derived from Olesen et al.[37]

pancreatic cancer (adjusted HR, 3.8) and colon cancer (adjusted HR, 2.1).[39]

The high frequency of PPDM-A after a single attack of (mild) acute pancreatitis has gained attention only during the past decade.[40] A 2015 population-based study from Taiwan showed a much higher risk of diabetes in people who had an attack of acute pancreatitis than those who did not (adjusted HR, 2.5).[15] Notably, this held true even when the analysis was constrained to people with mild acute pancreatitis only.[15] A 2020 population-based study from Israel similarly demonstrated an increased risk of diabetes in people who had an attack of acute pancreatitis than those who did not (adjusted HR, 2.1).[41] The LACERTA project (as part of the COSMOS program) – the first prospective longitudinal cohort study of unselected patients after an attack of acute pancreatitis that investigated glycemia at multiple time points and standardized intervals during follow-up – reported in 2020 the cumulative incidence of NODAP during the first 2 years after an attack of acute pancreatitis.[42] It increased notably from 3% at 6 months to 7% at 12 months, 9% at 18 months, and 11% at 24 months of follow-up. The study also found that severity of acute pancreatitis was not predictive of NODAP.[42] A 2019 population-based COSMOS study demonstrated that PPDM-A was associated with a significantly higher risk of developing psychiatric disorders (adjusted HR, 7.1) than acute pancreatitis without diabetes.[38] Given that the same study also found that recurrent acute pancreatitis and severe acute pancreatitis led to higher incidence of psychiatric disorders,[38] it remains to be investigated whether these characteristics of acute pancreatitis might contribute to the risk of psychiatric disorders in PPDM-A. A 2022 population-based study from Denmark showed that, in comparison with type 2 diabetes, PPDM-A was associated with significantly higher all-cause mortality (adjusted HR, 1.3; Figure 3).[37] A 2022 population-based study from South Korea reported similar findings (adjusted OR, 1.8).[17] PPDM-A was associated with a significantly higher risk of severe hypoglycemia (adjusted HR, 2.9) in the study from Denmark and hypoglycemia (adjusted OR, 1.9) in the study from South Korea.[17,37] A 2019 population-based COSMOS study found that, when compared with type 2 diabetes, PPDM-A was associated with increased mortality from cancer, infectious diseases, and gastrointestinal diseases.[36]

The combined burden of PPDM-C and PPDM-A was also investigated in nationwide population-based studies.[22,43] The incidence of PPDM was remarkably similar – 8 per 100,000 general population per year – in New Zealand and Denmark.[22,43] The mean time to new-onset diabetes was 56 months shorter in patients after a single attack of pancreatitis in comparison with those from the general population (who had no history of pancreatitis).[41] Remaining life expectancy was much lower in young and middle-aged adults with PPDM than those with type 2 diabetes.[39] Moreover, patients with PPDM had a significantly younger mean age at death than those with type 2 diabetes.[36] Modelling of future incidence of PPDM with the use of a time series approach estimated the average annual growth of 2.8%, reaching the incidence of 14 per 100,000 general population per year by 2050.[44] Also, the total years of life lost due to premature death in patients with PPDM was projected to increase by the year 2050, with the average annual growth of 3.2%.[44]

At-Risk Patients

Numerous high-quality studies during the past decade have challenged the restrictive and ossified view of NODAP in the past as diabetes caused only by massive destruction of β cells in the pancreas (due to extensive pancreatic necrosis or fibrosis).[21,29] Evidence has started to emerge that other pancreatitis-related characteristics may predispose to developing NODAP, although confirmatory studies are warranted for some of the risk factors discussed later in this article. A 2022 LACERTA study prospectively showed, for the first time, that glucose variability during hospitalization for acute pancreatitis accurately predicted the development of NODAP during follow-up.[45] Specifically, high glycemic lability index (calculated as the squared difference between 2 consecutive glucose measurements divided by the time between the measurements) during the first 72 hours after hospital admission for acute pancreatitis significantly increased the adjusted odds of developing NODAP by 13.7 times in the ensuing 24 months. At the same time, hyperglycemia at hospital admission was a much less accurate predictor of NODAP (adjusted OR, 2.2).[45] A 2015 population-based study from Taiwan showed that patients with 2 or more attacks of acute pancreatitis had a significantly higher risk of PPDM (adjusted OR, 1.9) in comparison with those who had 1 attack.[46] A 2021 population-based COSMOS study investigated the association between recurrent attacks of mild acute pancreatitis (and other biliary events) before cholecystectomy and the risk of PPDM.[47] It found that 3 or more recurrences were associated with the highest risk (adjusted HR, 2.8) of PPDM, followed by 2 recurrences (adjusted HR, 2.0). By contrast, 1 recurrence was not significantly associated with the risk of PPDM.[47] Severity of acute pancreatitis was consistently shown not to be associated with PPDM in both population-based and clinical studies.[15,42,46,48] Etiology of acute pancreatitis cannot be accurately ascertained in administrative databases and, therefore, there are no robust population-based studies on its association with PPDM risk.[21,49] However, a meta-analysis of clinical studies found no significant difference between alcohol-related and biliary etiologies of acute pancreatitis in terms of risk of PPDM.[40] The previously mentioned meta-analysis also found that severity of acute pancreatitis did not affect the risk of PPDM.[40]

When it comes to patients with chronic pancreatitis, several large retrospective studies consistently showed on multivariable analyses that pancreatic calcifications were associated with diabetes.[50–56] They were identified as an independent risk factor for diabetes among patients with pancreatitis in studies from France (risk ratio, 3.2),[50] the United States (OR, 2.6),[51] Sweden (HR, 2.4),[52] India (OR, 2.3),[53] China (HR, 2.3),[54] Scandinavia (OR, 1.5),[55] and Japan (risk ratio, 1.3).[56] Pancreatic calcifications were also

significantly associated with NODAP (adjusted HR, 2.0) in a time-to-event analysis.[53] Furthermore, change in glycated hemoglobin during a 6-month period differed significantly (in multivariable analysis) between patients with pancreatitis with pancreatic calcifications and those without them, with a marked increase in glycated hemoglobin observed only in patients with calcifications.[57] These findings justify designating pancreatic calcifications (that are not deemed to be vascular) as a major risk factor for NODAP. Pancreatic calcifications develop in the setting of high intracellular calcium levels as a result of alkaline hydrolysis of nonesterified fatty acids in the pancreas.[58] The predominant local source of the latter is intrapancreatic fat deposition, the key role of which in pancreatitis and its sequelae has been highlighted in the PANDORA (PANcreatic Diseases Originating from intRa-pancreatic fAt) hypothesis.[59]

Several patient-related characteristics are also associated with higher risk of PPDM. A 2021 cross-sectional study from Denmark, based on a prospectively maintained registry of more than 5000 well-phenotyped people with new-onset diabetes, showed that individuals with PPDM had significantly lower both general (as evidenced by body mass index [BMI]) and central (as evidenced by the waist-to-hip ratio) adiposity in comparison with type 2 diabetes individuals.[60] This finding was consistent with earlier population-based studies.[23,41] Specifically, a 2017 population-based study from the United Kingdom showed that, when compared with type 2 diabetes, a significantly higher proportion of PPDM-A was lean (adjusted OR, 1.6) and a significantly lower proportion was obese (adjusted OR, 0.8).[23] Furthermore, a 2020 study from Israel demonstrated a stronger risk of PPDM (adjusted OR, 3.1) when the overall cohort was constrained to individuals with normal BMI.[41] Another modifiable risk factor associated with PPDM is tobacco smoking. A multinational 2005 retrospective cohort study of patients with chronic pancreatitis found that smoking significantly increased the risk of developing PPDM (HR, 2.3) and this association was not materially affected by levels of alcohol consumption.[61] Similarly, tobacco smoking (but not alcohol consumption) was significantly associated with PPDM (HR, 2.9) in a 2011 study of patients with chronic pancreatitis from China.[54] Also, a 2023 study of chronic pancreatitis patients from the United States did not find alcohol etiology to be associated with a higher risk of PPDM.[51] A 2021 study of patients with chronic pancreatitis from India showed smoking to be significantly associated with higher cumulative probability of developing NODAP (adjusted HR, 2.4) as well as earlier onset of NODAP in a time-to-event analysis.[53] In a 2019 study from the United States, change in β-cell function (as evidenced by circulating levels of C-peptide) during a 6-month period was significantly different between acute and chronic pancreatitis patients with vs without tobacco smoking.[57] A significant decrease of β-cell function was observed only in patients with pancreatitis who were tobacco smokers. Moreover, a dose-dependent effect of tobacco smoking was found among smokers as greater number of pack-years was significantly associated with more rapid decrease in C-peptide.[57] Given that the study population was limited to patients who underwent total pancreatectomy with islet autotransplantation and there were no controls without pancreatitis by design,[57] it remains to be investigated whether the effect of smoking on β-cell function is independent of pancreatitis. The previously mentioned findings are generally in line with the results of a 2014 comprehensive COSMOS meta-analysis that identified tobacco smoking, but not alcohol consumption, as the strongest modifiable risk factor for diseases of the pancreas.[62]

Nonmodifiable (demographic) factors may also predispose to NODAP. Young and early middle-aged adults have a higher age-specific risk for PPDM than type 2 diabetes (although it is acknowledged that both types of diabetes are generally less common in these age groups in comparison with late middle-aged and older adults). A 2017 population-based study from the UK showed that individuals aged 20–29 had the highest age-specific risk for PPDM (OR, 4.2), followed by those aged 30–39 (OR, 1.7).[23] Similarly, a 2020 population-based study from Israel demonstrated that individuals younger than 40 years had the highest age-specific risk for PPDM (adjusted OR, 4.6).[41] In a 2021 population-based COSMOS study, individuals with PPDM younger than 45 years of age had significantly higher age-specific all-cause mortality than those with type 2 diabetes (adjusted HR, 2.1) and type 1 diabetes (adjusted HR, 2.9).[39] The strongest demographic factor is sex, with men being consistently shown to be disproportionately affected by PPDM. A 2015 population-based study from Taiwan showed that, while women had a 1.6 times higher risk of PPDM, the risk was 3.2 times higher for men.[15] This difference was statistically significant ($P < .001$).[15] A 2023 cohort study from the United States found that men had a 2.5 times higher risk of PPDM than women ($P < .001$).[51] Male sex was also associated with a greater risk of PPDM than type 2 diabetes in COSMOS (OR, 1.4),[63] Korean (OR, 1.2),[17] and Danish (risk ratio 1.2)[22] population-based studies.

Exocrine Pancreatic Insufficiency

Terminology and Classification

Exocrine pancreatic insufficiency (EPI) refers to a condition in which pancreatic secretion into the intestinal lumen is grossly inadequate for facilitating digestion. The main clinical signs of EPI are steatorrhea (oily and foul-smelling stool) and weight loss, which typically occur with ~90% loss of exocrine pancreatic function.[64] The corresponding presequela is exocrine pancreatic dysfunction (EPD) – a condition wherein pancreatic secretion into the duodenum is decreased below physiological level, yet not causing clinically overt maldigestion (Figure 2). The criterion standard for steatorrhea – the principal manifestation of EPI – is the coefficient of fat absorption that is <93% during a 72-hour fecal fat test (corresponding to >7 g of fecal fat excretion per 24 hours in a patient with 100 g of dietary fat intake per day; Table 1). This is the only criterion accepted by the American Food and Drug Administration and the European Medicines Agency for determining efficacy of pancreatic enzyme replacement therapy in clinical

trials.[65,66] However, the 72-hour fecal fat test is rarely performed in the clinic because it is labor-intensive and time-consuming. It follows that the assessment of exocrine function often relies on indirect tests, with the fecal elastase test currently being the most widely available tool. Different thresholds for normal exocrine pancreatic function have been investigated for this test, with levels <200 μg/g being the most frequently used in compliance with the "intended use" label (Table 1). It is worth noting that this threshold has relatively low specificity and, therefore, an abnormal level of fecal elastase may have a relatively high false-positive rate.[67] The same patient cannot simultaneously have both EPI and EPD, with the priority given to EPI (if a patient meets the criteria for both EPI and EPD) (Table 1).

Burden of Sequela

EPI is a common metabolic sequela of chronic pancreatitis, which develops in many patients as the disease progresses. The prevalence of EPI and EPD is ~50% in modern cross-sectional studies.[68,69] In earlier longitudinal cohort studies, the cumulative incidence of EPI and EPD was ~80% after 25 years from chronic pancreatitis diagnosis.[70–72] In a 2018 prospective longitudinal cohort study from Spain, including 430 patients with chronic pancreatitis followed up for a median of 8.6 years, EPI and EPD were identified as an independent risk factor for all-cause mortality (HR, 2.6).[73] The mechanisms linking EPI and EPD with excess mortality are incompletely understood. However, emerging evidence shows a link between exocrine function of the pancreas and intestinal dysbiosis, which in turn is associated with changes in glucometabolic pathways and sustained low-grade inflammation.[74,75] Such alterations may contribute to the increased risk of cardiovascular diseases and cancer observed in patients with pancreatitis.[76,77] Nutrient deficiencies secondary to EPI and malabsorption may also be implicated.[73,78,79]

In contrast to chronic pancreatitis, EPI and EPD in the context of acute pancreatitis have been less appreciated in the clinic. However, evidence from several meta-analyses during the past decade showed that the prevalence of EPI and EPD during first attack of acute pancreatitis is ~60%, decreasing to ~30% after 36 months.[80–82] The risk of developing EPI or EPD is not constrained to patients with extensive pancreatic necrosis, as almost half of patients with mild acute pancreatitis had EPI or EPD and one fifth of these patients had persisting EPI or EPD during long-term follow-up.[82]

At-Risk Patients

In patients with chronic pancreatitis, pancreatic calcifications were identified as a key pancreatitis-related risk factor for EPI and EPD.[70,72,83] In addition, surgical or endoscopic interventions may be associated with their presence, although the findings are inconsistent. Some studies found a beneficial effect of pancreatic duct decompression on exocrine pancreatic function whereas others did not.[84] It is conceivable that pancreatic resection leads to EPI or EPD due to acinar cell loss and this may be further accelerated by postprandial asynchrony between gastric emptying and exocrine pancreatic secretion (eg, after pancreaticoduodenectomy).[85] Patient-related (modifiable) risk factors for EPI and EPD include smoking and excessive alcohol consumption. In earlier retrospective cohort studies, patients with alcohol-related chronic pancreatitis were at high risk of EPI and EPD compared with patients with other etiologies.[70,72] However, in recent cohort studies, the association between excessive alcohol consumption and exocrine function was not evident when controlling for smoking. In contrast, smoking was an independent risk factor for EPI and EPD.[83,85,86] Specifically, tobacco smoking (HR, 1.6), but not alcohol consumption, was an independent risk factor for EPI after onset of chronic pancreatitis in a 2022 prospective cohort study from China.[85] Similarly, a 2022 retrospective cohort study of patients with chronic pancreatitis from Scandinavia found that tobacco smoking was independently associated (OR, 1.5) with EPD whereas alcohol consumption was not.[86] Also, smoking cessation (but not abstinence from alcohol) within 1 year of diagnosing chronic pancreatitis considerably reduced the risk of developing pancreatic calcifications during follow-up.[87] These observations suggest that earlier studies investigating the impact of alcohol on exocrine pancreatic function might have been subject to confounding by smoking. Among the nonmodifiable (demographic) factors, male sex is most strongly linked with EPI and EPD. The previously mentioned study from China showed that men with chronic pancreatitis had a 1.8 times higher risk of developing EPI than women.[85] In the nationwide COSMOS cohort of patients with chronic pancreatitis and acute pancreatitis, men were more likely to have EPD than women (OR, 1.5).[88]

In meta-analyses of small single-center studies, an approximately 2 times increase in the prevalence of EPD was observed in patients with acute pancreatitis with severe vs mild course of disease, and its prevalence was highest in the presence of pancreatic necrosis.[81,82] A 2014 COSMOS meta-analysis, pooling data from 8 cross-sectional studies, found that EPI and EPD were observed in 40% of patients with PPDM or prediabetes after acute pancreatitis.[80] However, the prevalence of concomitant derangements in both exocrine and endocrine functions decreased over time since diagnosis of pancreatitis, suggesting that exocrine pancreatic function may recover in some patients.[80] A 2021 population-based COSMOS cohort study showed that patients with EPD after first attack of acute pancreatitis were at an increased risk of PPDM (adjusted HR, 4.8).[88] This held true even in patients after mild acute pancreatitis alone (adjusted HR, 4.6). Importantly, the study used a 1-year lag period between diagnosing EPD and PPDM to minimize the possibility of reverse causality.[88] The mechanism linking abnormal exocrine pancreatic function and diabetes is not necessarily constrained to mechanical destruction of β cells in the pancreas but may also involve changes in the composition of gut microbiota and luminal pH (particularly in the duodenum due to reduced secretion of bicarbonate by

the pancreas), short-chain fatty acids (through the anerobic fermentation of indigested polysaccharides), iron metabolism, and bile acids signaling (through fibroblast growth factor 19 that has downstream insulin-like effects).[74,89–91]

Osteoporosis

Terminology and Classification

Osteoporosis is a condition characterized by low bone mass, increase in bone fragility, and susceptibility to fracture.[92] The corresponding presequela is osteopenia – low bone mineral density (BMD; Figure 2). The diagnostic criteria for osteoporosis and osteopenia are based on dual-energy X-ray absorptiometry. These criteria use standard deviation scores of BMD related to peak bone mass in healthy young adults (BMD T score) (Table 1).[93] However, the usefulness of BMD as a clinical indicator of osteoporosis is limited because BMD is only one of several risk factors for osteoporosis-related fractures. Indeed, most fragility fractures (ie, fractures resulting from low-energy trauma, such as a fall from standing height or less) occur in individuals with BMD values greater than the threshold for osteoporosis. Therefore, fragility fractures in the spine or hip are considered osteoporosis-defining fractures irrespective of BMD.[92]

Burden of Sequela

In a 2014 meta-analysis of 10 small single-center studies, the prevalence of osteoporosis in patients with chronic pancreatitis was 23% whereas 40% of patients had osteopenia.[94] In a 2018 multinational study of patients with chronic pancreatitis, the prevalence of osteoporosis was 22% and 42% of patients had osteopenia.[95] Comparable estimates were reported in a 2022 multicenter study from the United States: 17% of patients with chronic pancreatitis had osteoporosis and 39% had osteopenia.[96] Taken together, these data indicate that approximately 1 of 5 patients with chronic pancreatitis has osteoporosis, and more than half of patients have a bone mass less than normal. Three large cohort studies investigated the risk of fragility fractures in chronic pancreatitis.[97–99] A tertiary center study from the United States reported a significantly increased risk of fracture (OR, 2.4) in patients with chronic pancreatitis, compared with age, sex, and race-matched controls.[97] Notably, the fracture risk in chronic pancreatitis was similar to or higher than the fracture risk observed in other malabsorptive gastrointestinal diseases such as Crohn's disease and celiac disease.[97] In population-based studies the risk of fragility fracture was approximately 2 times higher in patients with chronic pancreatitis compared with matched controls.[98,99] By contrast with the wealth of studies on bone health in patients with chronic pancreatitis, there is a paucity of research in patients with acute pancreatitis. In a population-based study from Taiwan, the risk of osteoporosis was greater in patients with first attack of acute pancreatitis compared with matched controls (HR, 1.3), with a further heightened risk in patients with recurrent attacks of acute pancreatitis.[100]

At-Risk Patients

EPI and EPD were associated with low bone mass in 5 studies in the previously mentioned 2014 meta-analysis.[94] The mechanism linking abnormal exocrine pancreatic function and osteoporosis was thought in the past to be primarily related to malabsorption of micronutrients (including calcium and vitamin D). However, a 2016 meta-analysis did not find supportive evidence of significantly lower vitamin D levels in patients with chronic pancreatitis compared with controls.[101] Although this observation may be related to the difficulties of measuring and comparing vitamin D levels across studies, it could also indicate that the risk of low bone mass in chronic pancreatitis is driven by mediators beyond those related to malabsorption.[102,103] For example, diabetes and hypogonadism (possibly related to the use of opioids) have been associated with low bone mass in patients with pancreatitis.[104,105] The high risk of osteoporosis may also be linked to a sustained low-grade inflammation, which in turn leads to increased bone reabsorption.[106]

Other Metabolic Sequelae

Sarcopenia is a progressive and generalized skeletal muscle disorder characterized by impaired muscle function and decreased muscle mass. Muscle function is typically quantified using hand grip strength or chair stand test whereas muscle mass is typically quantified using bioelectrical impedance, dual-energy X-ray absorptiometry, computed tomography, or magnetic resonance imaging.[107] The 2019 European consensus guidelines on sarcopenia underline the importance of muscle strength as the key criterion for the diagnosis because it is recognized that muscle strength is better than muscle mass in predicting adverse clinical outcomes.[108] However, most studies on sarcopenia in patients with pancreatitis have been based solely on assessment of muscle mass. In a 2022 meta-analysis, the pooled prevalence of sarcopenia in patients with chronic pancreatitis was 32%.[109] The highest estimates were reported in studies of hospitalized patients (as opposed to outpatients) and in studies based exclusively on estimation of muscle mass without concomitant assessment of muscle function.[109,110] Some of the included patients with sarcopenia had a BMI in the obese range (ie, sarcopenic obesity).[110,111] In a 2020 COSMOS study, first attack of acute pancreatitis, recurrent acute pancreatitis, and chronic pancreatitis were significantly associated with progressively increased sarcopenia.[112] This finding was independent of age, sex, body fat distribution, physical activity, tobacco smoking, alcohol consumption, comorbidities, and exocrine and endocrine functions of the pancreas.[112] Several risk factors are implicated in the development of sarcopenia, some of which are patient-related (eg, advanced age and physical inactivity) whereas others are pancreatitis-related (eg, EPI).[107,111,113] Hyperleptinemia might be a mechanism underlying the observed associations because circulating levels of leptin (but not other major cytokines such as interleukin-6, tumor necrosis factor-α, and C-C motif chemokine ligand 2) were significantly inversely associated

with sarcopenia in patients with pancreatitis.[112] The impact of sarcopenia on clinical outcomes in patients with pancreatitis is just beginning to be investigated. In a 2019 study that followed patients with chronic pancreatitis during a 12-month period, sarcopenia was associated with reduced life quality, increased hospitalization rates, and excess mortality.[111] Sarcopenia was associated with a poor islet yield in a 2020 study of patients undergoing total pancreatectomy with islet auto-transplantation for chronic pancreatitis.[114] In a 2020 COSMOS study, sarcopenia in patients after pancreatitis was significantly associated with the presence of diabetes.[115] Furthermore, sarcopenia was associated with increased skeletal muscle fat deposition and decreased insulin sensitivity in these patients.[115]

Dyslipidemia can also develop after an attack of pancreatitis. Although the causative link between dyslipidemia (in particular, hypertriglyceridemia) and risk of acute pancreatitis has been well known since the 19th Century, derangements of lipid metabolism after an attack of acute pancreatitis have been scarcely investigated to date. A 1974 study showed that nearly three quarters of patients had elevated fasting levels of triglycerides several months after clinical resolution of acute pancreatitis (assumed to be alcohol-related).[116] Fasting levels of total cholesterol and phospholipids were within the reference range in most patients after an attack of acute pancreatitis in that study, yet significantly higher in comparison with controls. A 1985 study demonstrated that one quarter of patients had elevated fasting levels of triglycerides several months after clinical resolution of an attack of acute pancreatitis (mainly, biliary).[117] Furthermore, postprandial serum triglyceride levels were significantly higher for up to 24 hours after a high-fat meal in patients after an attack of acute pancreatitis than in controls, suggesting a decreased clearance of triglycerides from the circulation after an oral fat load. In both of the previously mentioned studies, derangements of lipid metabolism were not attributed to hyperchylomicronemia. A 2017 cross-sectional COSMOS study of patients after an attack of acute pancreatitis found that those with PPDM or prediabetes had significantly higher fasting levels of triglycerides and glycerol after hospital discharge in comparison with normoglycemic patients, consistently in all adjusted models.[118] However, the standard lipid panel measured at the time of hospitalization for acute pancreatitis was not significantly associated with the development of NODAP during follow-up in a 2020 prospective longitudinal LACERTA study.[42] In patients with definite chronic pancreatitis from Scandinavia, a 2020 retrospective cohort study identified hypertriglyceridemia as an independent risk factor (OR, 4.4) for diabetes.[55]

Gout in patients after first attack of acute pancreatitis was investigated in a 2020 population-based COSMOS study, with the cumulative incidence of gout in this population being 2.2%.[119] The study found that patients with PPDM were at a 1.9 times significantly higher risk for gout in the overall cohort. In the subgroup analysis stratified by sex, women with PPDM were at a 2.7 times significantly higher risk for gout whereas men did not have a significantly increased risk of gout. Patients with PPDM had a higher cumulative incidence of gout compared with patients with pancreatitis without PPDM; the highest risk was observed 6 years after first attack of acute pancreatitis.[119]

Metabolic Sequelae Surveillance Program

The high long-term burden of metabolic sequelae of pancreatitis highlighted in this article justifies surveillance of patients with pancreatitis. Pancreatic cancer surveillance in high-risk individuals began to be developed at the turn of the 21st Century and is widespread now.[120] There is now accumulating evidence that metabolic sequelae of pancreatitis should be afforded the same considerations. A mass surveillance of all patients with pancreatitis at regular intervals would, in theory, identify 100% of individuals who develop NODAP, EPI, and other sequelae at some stage in their lives. However, given that patients with pancreatitis are common, a surveillance program used indiscriminately is unlikely to be cost-effective and practical. Therefore, it is recommended that, in assessing the probability of developing an incident metabolic sequela, patients with pancreatitis are stratified into high-risk and low-risk groups based on certain criteria (Figure 4). The evidence is clear in regard to the associations between metabolic sequelae and pancreatic calcifications (after ruling out the possibility that calcifications are in blood vessels), tobacco smoking, and male sex. It is conceivable that other strong risk factors could be identified in the future.

Patients who fall into the high-risk group are eligible for the metabolic sequelae surveillance program (MSSP). Because the time-frame and order in which NODAP and EPI develop vary considerably from patient to patient,[80] the MSSP focuses on the 2 sequelae simultaneously. The start of surveillance is recommended at 6 months after pancreatitis diagnosis to enable identification of metabolic sequelae (or presequelae) in a timely manner (Figure 2). This is based on the findings of a 2020 prospective longitudinal LACERTA study where one fifth of patients with pancreatitis had new-onset prediabetes after pancreatitis or NODAP at 6 months of follow-up.[42] Earlier commencement of surveillance is not recommended to prevent the exhaustion of clinical resources due to premature enrollment of a large number of patients with transient hyperglycemia during the course of pancreatitis.[15,21] Furthermore, overdiagnosis of metabolic sequelae of pancreatitis (eg, when an abnormal parameter of diabetes is initially identified during hospitalization for pancreatitis but the NODAP criteria are not met until the first MSSP visit) may lead to overtreatment, absence of improvement in metabolic outcomes, as well as patient's psychological stress.[51] It is important that all patients with pancreatitis eligible for the MSSP have their glycated hemoglobin and fecal elastase measured during hospitalization (or initial outpatient clinic visit) to confirm that metabolic abnormalities detected during follow-up are new-onset. Subsequent surveillance during the initial period of MSSP is to be conducted on an annual basis (Figure 4). Patients with NODAP or EPI are to be referred to multidisciplinary review (involving, in addition to gastroenterologists,

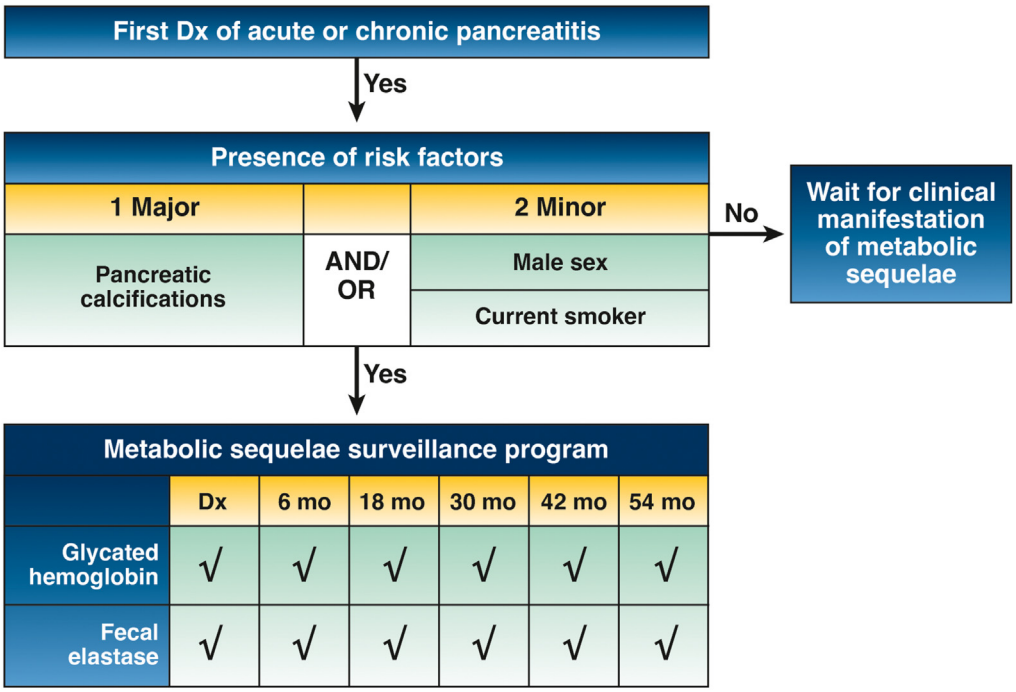

Figure 4. The MSSP in high-risk patients with pancreatitis. The present guideline applies to patients with pancreatitis with no pre-existing diabetes mellitus and exocrine pancreatic insufficiency. High-risk patients suitable for the MSSP are those with at least 1 major risk factor (pancreatic calcifications, providing that these are not in pancreatic blood vessels) or 2 minor risk factors (male sex, current tobacco smoker). Months refers to the time since Dx of first attack of pancreatitis. Only minimum guideline for the MSSP is presented with a view to facilitating its widespread adoption. Specialized pancreas centers may have an enhanced surveillance program.

endocrinologists, primary care physicians, dietitians, radiologists, and surgeons) of their cases for personalized care planning. Because NODAP and EPI are intricately linked, detection (and management) of one of them opens a window of opportunity for preventing the other during ongoing follow-up. Furthermore, given that the development of osteoporosis and other metabolic sequelae described in this article is strongly influenced by NODAP and EPI, the burden of the former can be reduced by identifying derangements in pancreatic endocrine and exocrine functions early.

Conclusions

The continuous expansion of knowledge about pancreatitis has put the spotlight in the 21st Century on the long-term consequences of this disease, the incidence of which is projected to increase.[44] Although NODAP, EPI, and other metabolic sequelae taken together have a heavy burden, each of them alone is avoidable in principle. A shift in the pancreatitis zeitgeist is anticipated in the upcoming decades, wherein patients with even an uneventful first attack of pancreatitis may undergo long-term surveillance after hospital discharge. The content and timeframe of the MSSP will require revision as new high-quality evidence becomes available. It is now time to accumulate experience from different parts of the world on the use of the MSSP in comparing outcomes of patients between different healthcare settings and evaluating the effects of interventions.

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