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Diagnosis and treatment of diabetes mellitus in chronic pancreatitis

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Abstract

Diabetes secondary to pancreatic diseases is commonly referred to as pancreatogenic diabetes or type 3c diabetes mellitus. It is a clinically relevant condition with a prevalence of 5%-10% among all diabetic subjects in Western populations. In nearly 80% of all type 3c diabetes mellitus cases, chronic pancreatitis seems to be the underlying disease. The prevalence and clinical importance of diabetes secondary to chronic pancreatitis has certainly been underestimated and underappreciated so far. In contrast to the management of type 1 or type 2 diabetes mellitus, the endocrinopathy in type 3c is very complex. The course of the disease is complicated by additional present comorbidities such as maldigestion and concomitant qualitative malnutrition. General awareness that patients with known and/or clinically overt chronic pancreatitis will develop type 3c diabetes mellitus (up to 90% of all cases) is rather good. However, in a patient first presenting with diabetes mellitus, chronic pancreatitis as a potential causative condition is seldom considered. Thus many patients are misdiagnosed. The failure to correctly diagnose type 3 diabetes mellitus leads to a failure to implement an appropriate

medical therapy. In patients with type 3c diabetes mellitus treating exocrine pancreatic insufficiency, preventing or treating a lack of fat-soluble vitamins (especially vitamin D) and restoring impaired fat hydrolysis and incretin secretion are key-features of medical therapy.

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Key words: Diabetes mellitus; Chronic pancreatitis; Type 3c diabetes; Pancreatogenic diabetes; Pancreatitis

Core tip: Type 3c diabetes mellitus is more common than generally thought. Its prevalence is supposed to be among 5%-10% among all diabetics. Most patients with type 3c diabetes mellitus suffer from chronic pancreatitis as the underlying disease. Misclassification of these patients is very common, yet identification of these patients is very important due to some special diagnostic and therapeutic considerations in this subset of patients. Among these are *e.g.*, restoring proper fat assimilation, preventing fat-soluble vitamin deficiency and early identification of pancreatic cancer patients. Specific diagnostic criteria for type 3c diabetes mellitus are proposed within this review.

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INTRODUCTION

Chronic pancreatitis is a disease characterized by pancreatic inflammatory and fibrotic injury resulting in irreversible parenchymal damage. Progressive nutrient maldigestion and disturbance of the timing and the interactions

Table 1 Current classification of diabetes mellitus

I	Type 1 Diabetes Mellitus (β -cell destruction, usually leading to absolute insulin deficiency) A: Immune mediated B: Idiopathic
II	Type 2 Diabetes Mellitus (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
III	Other Specific Types Of Diabetes Mellitus A: Genetic defects of β -cell function B: Genetic defects in insulin action C: Diseases of the exocrine pancreas 1: Pancreatitis 2: Trauma/pancreatectomy 3: Neoplasia 4: Cystic fibrosis 5: Hemochromatosis 6: Fibrocalculous pancreatopathy 7: Others D: Endocrinopathies E: Drug- or chemical-induced F: Infections G: Uncommon forms of immune-mediated diabetes H: Other genetic syndromes sometimes associated with diabetes
IV	Gestational Diabetes Mellitus

Source: Ref. [4,5], with permission.

between nutrient digestion and absorption is observed and may lead to severe metabolic derangements. Glucose intolerance and diabetes mellitus are observed quite frequently in the course of the disease^[1,2].

Development of diabetes mellitus in chronic pancreatitis mainly occurs due to the destruction of islet cells by pancreatic inflammation. Additionally, nutrient maldigestion leads to an impaired incretin secretion and therefore to a diminished insulin release of the remaining beta-cells^[3]. In contrast to the autoimmune mediated destruction of the beta-cells in type 1 diabetes mellitus, glucagon secreting alpha-cells and pancreatic polypeptide secreting pancreatic polypeptide-cells are also subject to destruction in chronic pancreatitis leading to a complex deranged metabolic situation.

Diabetes mellitus secondary to pancreatic diseases (such as chronic pancreatitis) is classified as pancreatogenic diabetes or type 3c diabetes mellitus according to the current classification of diabetes mellitus (Table 1)^[4,5]. Whereas the awareness of type 1 and type 2 diabetes mellitus is rather good, type 3c diabetes mellitus, however, is a condition rarely considered in everyday practice. Yet, recent data on type 3c diabetes mellitus show that it might be more common than generally thought. Studies also suggest that this important condition might be consistently under- and misdiagnosed^[6,7].

Due to the complex pathophysiology of type 3c diabetes mellitus it bears clinical and laboratory features which are very distinct from both type 1 and type 2 diabetes mellitus. This review focuses on diagnosis and treatment of diabetes mellitus secondary to chronic pancreatitis.

PREVALENCE OF DIABETES MELLITUS SECONDARY TO PANCREATIC DISEASES (TYPE 3C)

In contrast to type 1 and type 2 diabetes mellitus, detailed data on the prevalence of type 3c diabetes mellitus hardly exist. Some older studies estimate a rather low prevalence of about 0.5%-1.15% among all cases of diabetes mellitus in North America^[8,9]. Other studies from, *e.g.*, Southeast Asia where tropical or fibrocalcific pancreatitis is endemic, report a higher prevalence of approximately 15%-20% of all diabetes mellitus cases^[10,11].

A recent review of the currently available studies on this topic proposes a prevalence of 5%-10% for type 3c diabetes mellitus among all diabetes mellitus cases in Western populations^[12]. Data are mainly based on a large retrospective study of 1868 patients at a German University Hospital, where type 3c diabetes mellitus accounted for 9.2% of all diabetics^[7]. This emphasizes that previous older estimates of the prevalence of type 3c diabetes mellitus must be inaccurately low. In 78.5% of all patients with type 3c diabetes mellitus, chronic pancreatitis was identified as the underlying diseases, therefore resembling the most important causative condition^[7].

The previous underestimation of the prevalence of type 3c diabetes mellitus might partly be due to the fact that investigation of the pancreas has meanwhile been facilitated by new diagnostic procedures. Nowadays it has become much easier to detect exocrine pancreatic pathology as imaging methods of the pancreas have clearly improved and noninvasive screening methods to quantify exocrine pancreatic insufficiency are easily available.

If chronic pancreatitis accounts for nearly 80% of all type 3c diabetes mellitus cases, and if the prevalence of type 3c diabetes mellitus is expected to be approximately 5%-10% of all diabetes mellitus cases, the true prevalence of (subclinical) chronic pancreatitis in the general population seems to be far underestimated. This might especially hold true since chronic pancreatitis has previously been considered a disease of alcoholism until the discovery that it is a multifactorial disease with an impact of complex genetic genotypes, smoking, special anatomic conditions, toxic agents and autoimmunity, also^[13]. Up to date quite a few autopsy studies^[14-16], endoscopic ultrasound studies^[17] and exocrine pancreatic function studies^[18] report a high frequency of exocrine pancreatic injury suggestive of chronic pancreatitis in the general population. This further supports the view of an underestimation of chronic (subclinical) pancreatitis in the general population.

DIAGNOSIS OF DIABETES MELLITUS IN CHRONIC PANCREATITIS

As stated above glucose intolerance and diabetes mellitus are common in chronic pancreatitis. Diagnosing diabetes

Table 2 Proposed diagnostic criteria for type 3c diabetes mellitus

Major criteria (must be present)
Presence of exocrine pancreatic insufficiency (monoclonal fecal elastase-1 test or direct function tests)
Pathological pancreatic imaging (endoscopic ultrasound, MRI, CT)
Absence of type 1 diabetes mellitus associated autoimmune markers
Minor criteria
Absent pancreatic polypeptide secretion
Impaired incretin secretion (<i>e.g.</i> , GLP-1)
No excessive insulin resistance (<i>e.g.</i> , HOMA-IR)
Impaired beta cell function (<i>e.g.</i> , HOMA-B, C-Peptide/glucose-ratio)
Low serum levels of lipid soluble vitamins (A, D, E and K)

MRI: Magnetic resonance imaging; CT: Computed tomography; GLP-1: Glucagon-like peptide-1; HOMA-IR: Homeostasis model assessment of insulin resistance; HOMA-B: Homeostasis model assessment of beta-cell.

mellitus in a patient with known chronic pancreatitis may not be that difficult. Yet, the correct classification of type 3c diabetes mellitus is often missed and patients are commonly misclassified. In a German study only about half of the cases of type 3c diabetes mellitus were classified correctly. Type 3c diabetes mellitus patients were mostly misclassified as type 2 diabetes^[7]. This might be due to the very poor awareness of this diabetes type.

However, another thing appears even more difficult: do not forget to take into account that a patient first presenting with diabetes mellitus might have a type 3c diabetes mellitus. In any case of a new diabetes mellitus manifestation we should truly use the classification criteria defined by the European Association on the Study of Diabetes (EASD) and the American Diabetes Association (ADA)^[4,5] and check for type 3c diabetes mellitus. At least if a patient does not fit into the common presentation and complains about gastrointestinal symptoms the physician should be aware of the existence of type 3c and initiate further diagnostics.

Screening for type 3c diabetes mellitus in chronic pancreatitis

Any patient with chronic pancreatitis should of course be monitored for the development of type 3c diabetes mellitus. The prevalence of diabetes mellitus among patients with an established diagnosis of chronic pancreatitis is reported to be up to 70% (in chronic calcific pancreatitis even up to 90%)^[1,2]. Patients with long-standing duration of the disease, prior partial pancreatectomy, and early onset of calcific disease seem to be at higher risk for developing type 3c diabetes mellitus. There is a clear increase in the prevalence with the duration of chronic pancreatitis^[19,20].

The initial evaluation of patients with chronic pancreatitis should include fasting glucose and HbA_{1c}. These tests should be repeated at least annually. Impairment in either one requires further evaluation. If testing suggests an impaired glucose tolerance, further evaluation by a 75 g oral glucose tolerance test is recommended^[21]. A concomitant analysis of insulin and/or C-peptide levels may be help-

ful in distinguishing between type 2 and type 3c diabetes mellitus^[22].

Distinguishing type 3c diabetes from other types

It is not always easy to diagnose and classify a patient with type 3c diabetes mellitus correctly. Long-standing type 1 and type 2 diabetes mellitus patients are associated with exocrine pancreatic failure^[23] and patients with diabetes mellitus are at a higher risk for developing acute and/or chronic pancreatitis anyway^[24,25]. Patients with previous episodes of pancreatitis may also develop type 1 or type 2 diabetes independently of their exocrine pancreatic disease. In order to classify patients with type 3c diabetes mellitus correctly, commonly accepted diagnosis criteria should be established.

In distinguishing between the different diabetes types the presence of islet cell antibodies is consistent with type 1 diabetes mellitus, and the presence of clinical or biochemical evidence of insulin resistance is associated with type 2 diabetes mellitus. Due to the lack of commonly accepted diagnostic criteria up to date, we propose the following criteria for diagnosing type 3c diabetes mellitus (Table 2).

The evaluation of pancreatic polypeptide response to insulin-induced hypoglycemia, secretin-infusion or a mixed nutrient ingestion might be of additional diagnostic interest as discussed elsewhere^[21]. An absent pancreatic polypeptide response is able to distinguish between type 3c diabetes mellitus from early type 1 and may also distinguish type 3c from type 2, which is characterized by elevated pancreatic polypeptide levels^[26-28]. Routinely testing of incretin secretion or pancreatic polypeptide response in everyday practice, however, does not seem feasible.

TREATMENT OF DIABETES MELLITUS SECONDARY TO CHRONIC PANCREATITIS

Managing hyperglycemia

The derangement in glucose metabolism in type 3c diabetes mellitus ranges from a mild impairment to a severe form characterized by frequent episodes of hypoglycemia, commonly referred to as brittle diabetes^[9]. In type 3c diabetes mellitus, blood glucose control may be unstable due to the loss of glucagon response to hypoglycemia, carbohydrate malabsorption and/or inconsistent eating patterns due to concomitant pain and/or nausea or chronic alcohol abuse. Thus it is generally reported that type 3c diabetes mellitus is difficult to control, although there are only very few studies in this field^[29,30]. Astonishingly, all large clinical trials, including Diabetes Control and Complications Trial^[31] and United Kingdom Prospective Diabetes Study^[32] specifically excluded patients with type 3c diabetes mellitus.

Currently, there are no generally accepted guidelines

regarding treatment pathways for type 3c diabetes mellitus. Yet, a first step was taken at Pancreas Fest 2012^[21]. The pharmacological agents typically used for the treatment of type 3c diabetes mellitus are the same as for type 2 diabetes mellitus. The ADA and the EASD recommend metformin as the first-line oral therapy for type 2 diabetes mellitus^[33]. Therefore many type 3c diabetes mellitus patients are initially treated with metformin as a drug of first choice. If hyperglycemia is rather mild and concomitant insulin resistance is additionally diagnosed or suspected, therapy with metformin may be a good choice in the absence of contraindications. However, metformin treatment might not be tolerated by a majority of patients since its main side effects include nausea, abdominal complaints, diarrhea and weight reduction. A patient with chronic pancreatitis will probably not tolerate these symptoms. Since metformin therapy proves capable of reducing the risk of pancreatic cancer by as much as 70%, however, its anti-diabetic and anti-neoplastic effects may be beneficial in patients with type 3c diabetes mellitus due to chronic pancreatitis^[34]. This holds especially true since chronic pancreatitis and diabetes mellitus are both well accepted risk factors for the development of pancreatic cancer^[35-37].

Incretin based therapies [*e.g.*, glucagon-like peptide-1, (GLP-1)-analogues, dipeptidyl peptidase (DPP)-IV-inhibitors] also enhance insulin secretion. Yet, GLP-1-analogues as well as DPP-IV-inhibitors are both associated with a higher risk of pancreatitis and are reported to have a high frequency of prominent gastrointestinal side effects (*e.g.*, nausea, delayed gastric emptying, weight loss)^[38]. Therefore their use should best be avoided at present time until their safety is confirmed. A better and probably safer way to positively influence the incretin system might be a proper supplementation with pancreatic enzymes in these patients as discussed below.

In early type 3c diabetes mellitus, oral therapy with insulin secretagogues (sulfonylurea and glinides) may also be considered, thiazolidines should be avoided due to prominent side effects (*e.g.*, bone fractures, fluid retention, congestive heart disease).

Chronic pancreatitis, however, must be seen as a progressive disorder and many patients will eventually require insulin therapy. Patients should then be treated using general insulin dosing guidelines as established for type 1 diabetes mellitus. In patients with severe malnutrition insulin therapy is commonly used as a therapy of first choice. This is due to the desired anabolic effects of insulin in this special subset of patients.

Insulin pump therapy may also be considered for patients who experience a brittle form of diabetes mellitus despite being sufficiently motivated.

As it is in the other diabetes types, initial treatment should include all efforts to correct lifestyle factors which contribute to hyperglycemia and the risk of pancreatic malignancy (*e.g.*, abstinence from alcohol and smoking cessation, weight loss in overweight subjects, physical exercise and dietary modifications).

Managing exocrine pancreatic insufficiency

Many patients with chronic pancreatitis manifest some degree of fat malabsorption, regardless of the presence of symptoms. In patients with type 3c diabetes mellitus exocrine pancreatic insufficiency is nearly ubiquitous present. Since clinically overt steatorrhea is usually not observed until over 90% of exocrine pancreatic function have vanished, exocrine pancreatic insufficiency and maldigestion might remain undetected. However, the relevant maldigestion, which is present in the majority of patients with chronic pancreatitis, may cause qualitative malnutrition. This is especially important concerning the absorption of fat-soluble vitamins (A, D, E and K).

Very recent studies show a vitamin D deficiency in > 90% of patients with chronic pancreatitis^[39,40]. Additionally a significant correlation of exocrine pancreatic insufficiency and osteoporosis and/or alterations in bone metabolism can be observed^[41,42].

Further considering the possible role of vitamin D deficiency in the pathogenesis of type 1 diabetes mellitus and the association of low vitamin D levels and poor glycemic control in observational studies^[43,44], qualitative malnutrition of vitamin D in patients with type 3c diabetes mellitus seems of clinical importance. Measuring serum-25-hydroxyvitamin D levels and supplementing deficient patients might thus be beneficial.

The incretin system may play another crucial role in the metabolic control of type 3c diabetes mellitus. The regulation of the beta-cell mass and the physiological incretin secretion are directly dependent on normal exocrine pancreatic function and fat hydrolysis. Chronic pancreatitis and exocrine dysfunction have been associated with a functional impairment of the incretin system. Impaired GLP-1 secretion, however, can be normalized by pancreatic enzyme supplementation as previously described^[3,45,46].

Adequate oral pancreatic enzyme replacement therefore seems very important in type 3c diabetes mellitus. Besides helping to control symptoms of steatorrhea, it also seems capable of preventing qualitative malnutrition and metabolic complications.

CONCLUSION

Type 3c diabetes mellitus is a clinically important disease with a prevalence of 5%-10% among all patients with diabetes mellitus. The prevalence and clinical importance of this condition has been underestimated and underappreciated in the past.

Most patients with type 3c diabetes mellitus suffer from chronic pancreatitis as the underlying disease. The prevalence of (subclinical) chronic pancreatitis might also be underestimated as some studies suggest. Recognizing a diabetic state in patients with known chronic pancreatitis is obligatory. Patients should undergo screening tests in order to detect hyperglycemia early. Fasting glucose, HbA_{1c} and 75 g oral glucose tolerance testing are appropriate diagnostic tools. When diagnosing diabetes

mellitus in patients with chronic pancreatitis, physicians should be aware of the existence of type 3c diabetes mellitus and should classify this condition correctly as pancreatogenic diabetes or type 3c diabetes mellitus.

To identify a (subclinical) chronic pancreatitis as the underlying condition of patients with the established diagnosis of diabetes mellitus certainly is the greater challenge in everyday practice. This is due to the fact that most physicians are not aware of type 3c diabetes mellitus and (subclinical chronic) pancreatitis does not necessarily present in a clinically impressive manner. A patient with unspecific gastrointestinal complaints and diabetes mellitus should therefore always prompt further diagnostics with regard to type 3c diabetes mellitus.

Identifying patients with type 3c diabetes is important since the endocrinopathy in type 3c diabetes is very complex and complicated by additional present comorbidities such as maldigestion and concomitant qualitative malnutrition. Specific diagnostic criteria are proposed above (Table 1). The failure to correctly diagnose type 3c diabetes mellitus leads to failure to implement an appropriate medical therapy. It is mandatory to treat pancreatic exocrine insufficiency in these patients even if clear clinical symptoms such as steatorrhea or gastrointestinal complaints are missing. Adequate pancreatic enzyme supplementation therapy might for once help preventing a lack of fat-soluble vitamins (especially vitamin D). Additionally it might exert beneficial effects on the impaired incretin release in patients with chronic pancreatitis. Furthermore one has to realize that type 3c diabetes mellitus due to chronic pancreatitis might be referred to as a pre-malignant condition since both diseases are well accepted risk factors for the development of pancreatic cancer.

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