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REVIEW

The nutritional management of type 3c (pancreatogenic) diabetes in chronic pancreatitis

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Type 3c diabetes mellitus (T3cDM), also known as pancreatogenic diabetes, refers to diabetes caused by disease of the exocrine pancreas. T3cDM is not commonly recognised by clinicians and frequently it is misclassified as T1DM, or more commonly, T2DM. T3cDM can be difficult to distinguish from T1DM and T2DM, and it often co-exists with the latter. The aim of this review is to describe T3cDM, along with its complications, diagnosis and management. We focus on the nutritional implications of T3cDM for those with chronic pancreatitis, and provide a practical guide to the nutritional management of this condition.

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INTRODUCTION

Diabetes mellitus is defined as a group of metabolic diseases characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action or both.[1] The mortality associated with diabetes is considerable, and in fact diabetes is the seventh leading cause of death in the United States, and those with diabetes have double the overall risk of death than those without. This condition brings considerable long-term complications: retinopathy with potential blindness; nephropathy with potential renal failure; peripheral neuropathy with potential for ulceration and amputation; autonomic neuropathy associated with gastrointestinal, genitourinary, cardiovascular symptoms and sexual dysfunction; and increased incidence of atherosclerotic cardiovascular, peripheral arterial and cerebrovascular disease.[1] Consequently, both diabetes and prediabetes carry a considerable socioeconomic burden. Therefore, early diagnosis and tight glycaemic control are crucial. According to the American Diabetes Association (ADA), there are four subtypes of diabetes.[1] This review focusses on type 3c diabetes (T3cDM, also known as pancreatogenic or apancreatic diabetes) in both acute and chronic pancreatitis, and describes emerging developments and guidelines on the nutritional management of this condition.

SUBGROUPS OF DIABETES

Type 1 diabetes (T1DM) is immune mediated or idiopathic, and is characterised by beta-cell destruction usually leading to absolute insulin deficiency. Type 2 diabetes (T2DM) is regarded as a spectrum ranging from insulin resistance with relative insulin deficiency to a secretory defect with insulin resistance. In the ADA guidelines, 'other specific types of diabetes' are listed as type 3 diabetes, and among this group, T3cDM encompasses diseases of the exocrine pancreas. Type 4 diabetes refers to gestational diabetes.[1]

While clinicians are well aware of types 1 and 2, a retrospective study[2] of almost 2000 diabetes patients in a German hospital[2] found that patients with T3cDM tended to be misclassified, usually as T2DM. In fact, about 8% of all diabetes patients were correctly reclassified (according to the ADA classification) as T3cDM, of which patients with chronic pancreatitis were in the majority (76%). The remainder were patients with pancreatic neoplasia (9%), haemochromatosis (8%), cystic fibrosis (4%) and pancreatic resection (3%). The authors suggested that diabetes secondary to pancreatic conditions is more common than generally thought.

Although T3cDM has features of both T1DM and T2DM, it is distinct from both. For example, in common with T2DM, ketoacidosis is rare and hyperglycaemia is (usually) mild. Cui and Andersen[3] stated that glucagon-like peptide-1 levels are normal or high in T2DM; however, studies show that glucagon-like peptide-1 levels tend to be low or normal in T2DM,[4] increasing with metformin therapy or the commencement of pancreatic enzyme replacement therapy (PERT).[5] Conversely, glucagon-like peptide-1 levels are reportedly high or normal in T3cDM.[6] In common with T1DM, hypoglycaemic events are frequent, and insulin levels are low.[3,7]

DIAGNOSIS OF T3CDM

To diagnose T3cDM (as for types 1 and 2), an initial evaluation includes fasting glucose levels and glycated haemoglobin (HbA1c or A1c), and impairment in either should mandate further evaluation.[1] According to the recent criteria of the ADA, a fasting plasma glucose level of $\geqslant$126 mg/dl (7 mmol/l) or an HbA1c of $\geqslant$48 mmol/mol (6.5%) indicates diabetes; while a fasting plasma glucose of 100–125 mg/dl (5.6–6.9 mmol/l) or an HbA1c of 39–46 mmol/mol (5.7–6.4%) indicates an increased risk of diabetes ('prediabetes').[1,8] Where equivocal, impairment of either fasting glucose or HbA1c should be followed by a 75-g oral glucose tolerance test. However, discerning T3cDM from types 1 and 2 is not always clear cut, and in fact, both T2DM and T3cDM can co-exist.[9] Ewald and Hardt[6] suggested that the following major criteria must be present for a diagnosis of T3cDM: pancreatic exocrine insufficiency (PEI), pathological pancreatic imaging, along with an absence of T1DM-associated autoimmune markers. In addition, they proposed a number of minor criteria including the absence of pancreatic polypeptide (PP) secretion, impaired incretin secretion, no excessive insulin resistance (homeostatic

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model assessment of insulin resistance, HOMA-IR), impaired beta-cell function (measured by HOMA-B or glucose:c-peptide ratio) and low serum levels of lipid-soluble vitamins.

However, the specific details of such criteria remain uncertain. For example, the precise definition or referent for insulin resistance is debatable. Stern *et al.*[10] suggested that a subject is insulin resistant if HOMA-IR is >4.65, or body mass index is >28.9 kg/m^2, or HOMA-IR is >3.68 and body mass index is >27.5 kg/m^2, but there may be other reference ranges for other population and patient types. Similarly, the optimal timing of laboratory testing is open to question, Meier *et al.*[11] reported that a glucose:c-peptide at 15 min post glucose ingestion represents a better estimate of beta-cell area than even a fasting ratio, and this study reported that there was in fact no relationship between beta-cell area and the HOMA-B index. In addition, T1DM or T2DM patients with severe autonomic neuropathy may have markedly reduced or absent PP responses,[12] which should be borne in mind when using PP response as a diagnostic criterion. Furthermore, not all patients with chronic pancreatitis have fat-soluble vitamin deficiencies, and in fact, some studies have reported that only a minority of subjects have deficiencies.[13,14] Treatment with PERT and replacement of vitamins, if found to be low, means that this minor criterion may only be true in a minority of cases and unlikely to be useful as a means of diagnosing T3cDM. Accepting the above caveats, the diagnostic criteria by Ewald and colleagues remain the best estimation at diagnosis of T3cDM to date.

T3cDM develops in the setting of both insulin deficiency and PP deficiency, and the latter is partially responsible for hepatic insulin resistance.[3] PP is secreted predominantly by the cells in the head of the pancreas, and is promptly secreted in response to ingested nutrients. Those who undergo pancreatectomy, or proximal pancreatic resection are PP deficient. However, PP deficiency alone does not result in diabetes, but is associated with glucose intolerance and hepatic insulin resistance.[3] To more reliably discern T3cDM from types 1 and 2, an absent PP response to a mixed-nutrient meal might be a useful test.[6] Unlike a mixed-nutrient meal or liquid, glucose alone is a relatively weak stimulator of PP.[15] Definitive criteria for the analysis of the PP response to nutrients are not established; however, non-diabetic subjects may exhibit a four- to six-fold increase over basal levels. Those with chronic pancreatitis-associated diabetes could exhibit a less than two-fold increase from baseline levels.[3] T2DM is typically associated with an increase in both basal and stimulated levels of PP.[15]

However, it is not feasible to expect the PP response to a mixed-nutrient ingestion to be performed for all patients; and therefore, the following laboratory results should be done at least once to classify the patient as well as possible: diabetes-associated autoantibodies (to distinguish from T1DM), c-peptide:glucose ratio and HOMA-IR, as well as assessments of pancreatic exocrine function and pancreatic imaging. The measurement of pancreatic exocrine function may be done directly or indirectly. Direct testing involves collection of pancreatic secretions via duodenal intubation following pancreatic stimulation using secretin-CCK, and while this is the gold standard in terms of specificity and sensitivity, it is also difficult, invasive, expensive and hence rarely done outside specialist research centres. Indirect tests include the 3-day faecal fat test and faecal elastase-1, the latter being easy, convenient and widely available, although it is inaccurate for mild/moderate PEI. Other indirect tests include the ^{13}C breath test, which measures the amount of ^{13}C released following a meal of labelled ^{13}C-triglyceride. In PEI, there is a reduction in ^{13}C released.[16] More recently, the measurement of serum micronutrient deficiency as a means of assessing PEI has been described.[17]

MANAGEMENT AND TREATMENT GOALS

In the absence of studies specifically investigating the treatment of T3cDM, the current guidelines for management are inferred from best practice as applied to T1DM and T2DM. In fact, there is a severe dearth of studies focusing specifically on the management of those with T3cDM, and indeed, subjects with pancreatogenic diabetes tended to be specifically excluded from many diabetes studies. In basic terms, the goals of management are to reduce fasting glucose to 70–30 mg/dl (3.9–7.2 mmol/l), and HbA1c to <53 mmol/mol (7%), although patient-specific management with individualised therapy goals according to the patient's situation (such as age, co-morbidities and life expectancy) is recommended. Cui and Andersen[3] recommended that for all patients, concerted effort is required to correct lifestyle factors, specifically weight loss in obese subjects, daily exercise, a diet limited in carbohydrates, abstinence from alcohol and smoking cessation. However, even within the T3cDM classification subgroup, there are several different patient types with wildly diverse clinical concerns and management priorities. The nutritional considerations for the management of pancreatitis-associated T3cDM are discussed below.

CHRONIC PANCREATITIS

Chronic pancreatitis is a chronic inflammatory disease of the pancreas characterised by irreversible morphological change and typically causing pain and/or permanent loss of function.[18] The disease is characterised by the destruction of healthy pancreatic tissue and the development of fibrous scar tissue leading to abdominal pain, and a progressive loss of exocrine/endocrine function, and therefore steatorrhea, malnutrition and eventually diabetes. The incidence of chronic pancreatitis in Europe is reportedly 6–7 per 1 00 000,[19] and studies suggest that this is increasing.[20] The majority of cases from western countries have been attributed to alcohol excess, although aetiologies vary by region and country.

Pathophysiology and prevalence

Diabetes develops in chronic pancreatitis mainly as a consequence of the destruction of islet cells by pancreatic inflammation. In addition, nutrient maldigestion leads to an impaired incretin secretion and therefore to a diminished insulin release from the remaining beta-cells.[21] Diabetes is a common complication of chronic pancreatitis with a broad prevalence of 5 to >80% depending largely on aetiology, geography and duration of follow-up. The risk of developing diabetes rises with increasing age,[22,23] longer duration of disease,[24,25] heavy smoking,[26–28] the presence of pancreatic calcifications,[23,25,29] and in those who have had pancreatic resection, especially distal pancreatectomy.[25] Those who develop diabetes are likely to also have exocrine impairment.

Brittle diabetes

Up to 25% of patients with chronic pancreatitis-related T3cDM have 'brittle diabetes', characterised by rapid swings in glucose.[30–32] Hyperglycaemia commonly occurs (due to unsuppressed hepatic glucose production), which may be followed by severe hypoglycaemia due to administration of exogenous insulin, enhanced peripheral insulin sensitivity and a reduced secretion of the counter-regulatory hormone, glucagon. The risk of hypoglycaemia may be further increased due to poor dietary intake (as a consequence of pain or avoidance of adverse symptoms), exocrine insufficiency causing malabsorption, and for some, persistent alcohol intake.[33] Therefore, due to labile glucose control these patients are generally considered to be difficult to manage, not least dietary management. However, not all patients with chronic pancreatitis are classically malnourished, and in fact, many are overweight or obese with associated insulin resistance.[13] Therefore, it is likely that some patients with chronic

pancreatitis-associated diabetes have a condition that has more in common with T2DM than with T3cDM, and should therefore be managed as such. Overweight and obesity should be addressed and patients should be educated regarding the importance of a healthy, balanced diet to aid gradual weight loss.

Complications of T3cDM

The incidence of diabetes-related complication in T3cDM is thought to be similar to that of T1DM and T2DM, including retinopathy, renal dysfunction, neuropathy and microangiopathic complications. There is a general acceptance that macrovascular complications are not as common in T3cDM due to poor dietary intake and PEI; however, the data are unclear and more long-term research is warranted to properly analyse the risks.

Dietary management of T3cDM in chronic pancreatitis

Up to recently, there were no guidelines relating specifically to the management of T3cDM, and the first guideline document was published following Pancreas Fest in 2012.[9] This document provided much needed guidance on the distinction of T3cDM from T1DM and T2DM, the evaluation and management of the condition in the context of current endocrine practice, as well as a discussion of the pathophysiology of T3cDM. However, there was not a great deal of attention given to the dietary evaluation and management of those with T3cDM.

The ADA guidelines on the standards of Medical Care in Diabetes that describe the assessment and management of T1DM and T2DM (but not T3cDM) recommended an individualised medical nutrition therapy programme by a registered dietitian. Furthermore, each person with diabetes should actively engage with self-management, education and treatment planning with his/her health-care team, including the collaborative development of an individualised eating plan.[34]

In the first instance, dietary management should prioritise the prevention of hypoglycaemic events, which may frequently occur. Patients should be educated on the importance of maintaining a regular eating pattern with the inclusion of starchy carbohydrate foods. The importance of not skipping meals should be emphasised. Patients should be educated on the symptoms and treatment of hypoglycaemia as for T1DM. Blood glucose levels should be monitored regularly. A blood glucose level of < 72 mg/dl (< 4 mmol/L) should always be treated, even the patient is asymptomatic. For T1DM and T2DM patients on intensive insulin regimens, the ADA[35] have recommended self-monitoring of blood glucose 6–10 times per day (or more). While T3cDM was not discussed, these recommendations could be extrapolated for those with T3cDM on intensive insulin regimens. Specifically, they suggested testing before meals and snacks, occasionally post-prandially, at bedtime, before exercising, when low blood glucose is suspected, after treating for low blood glucose until normoglycaemia is achieved, and before critical tasks such as driving. The ADA suggested that the evidence for frequency of testing is insufficient for those on basal insulin regimens or on oral medications.

Careful monitoring and recording of blood sugar levels, diet, exercise and PERT might help those with 'brittle diabetes' in particular. The maintenance of a detailed diet and blood glucose diary should be recommended to aid in dietary reviews.[33] Those with alcohol-related chronic pancreatitis (who continue to drink) are more likely to experience hypoglycaemia,[34] and the risks are augmented with poor dietary intake, missing meals, taking too much insulin, higher-than-normal physical activity, after vomiting or poor compliance with PERT resulting in malabsorption.[6] It is very important to address alcohol intake with this patient group,[36] and the consequences of continued alcohol consumption should be clearly explained.

The next dietary priority should be to amend the diet to reduce the degree and frequency of hyperglycaemia, aiming to minimise the risks associated with complications of diabetes.[33] The consumption of simple sugars and refined carbohydrates should be curtailed, and in general a low-glycaemic index diet should be followed. Sugary drinks should especially be avoided, unless treating an episode of hypoglycaemia. 'Diabetic foods', or foods (such as diabetic chocolate) specifically marketed at those with diabetes are generally not recommended as they are expensive and may have a laxative effect if taken in excessive amounts.

For those with concomitant PEI (and most patients with pancreatitis-associated diabetes will also have PEI), it is vital that patients are taking appropriate and adequate amounts of PERT to ensure optimal nutrient absorption. Assessment of compliance is important and patients should be made aware of the signs and symptoms of malabsorption, which may include flatulence, abdominal pain, weight loss, nausea, reflux and bloating, as well

Table 1. Adapted from 'suggested principles of management and management strategies for type 3c diabetes in chronic pancreatitis'

Principles of management	*Management strategies*
Prevent:	• Regular meal pattern with regular starchy carbohydrates
• Hypoglycaemia	• Do not skip meals
• Hyperglycaemia	• Take small, frequent meals
• Exacerbation of malnutrition	• Measure glucose levels frequently, particularly if on insulin, after physical activity, if diet is poor, and if any hypoglycaemic symptoms
• Co-morbidities associated with diabetes (e.g., retinopathy and renal disease)	• Avoid alcohol, smoking cessation
	• Ensure adequacy of enzyme therapy
	• Minimise high-sugar/high-glycaemic index food or fluids
	• Consider a diary to record diet, glucose levels, enzymes, exercise, at least until acceptable glucose control is maintained
	• Routine dietitian assessment/monitoring

Reprinted with permission from Duggan and Conlon.[33]

as the obvious symptoms of fat malabsorption. Bloating and excessive flatus in particular may be symptoms of the colonic fermentation of malabsorbed carbohydrate, which may salvage up to 10% of total energy.[37] It should be borne in mind that after establishing PERT in a patient with severe malabsorptive symptoms, diabetes may in fact be 'unmasked', as the patient

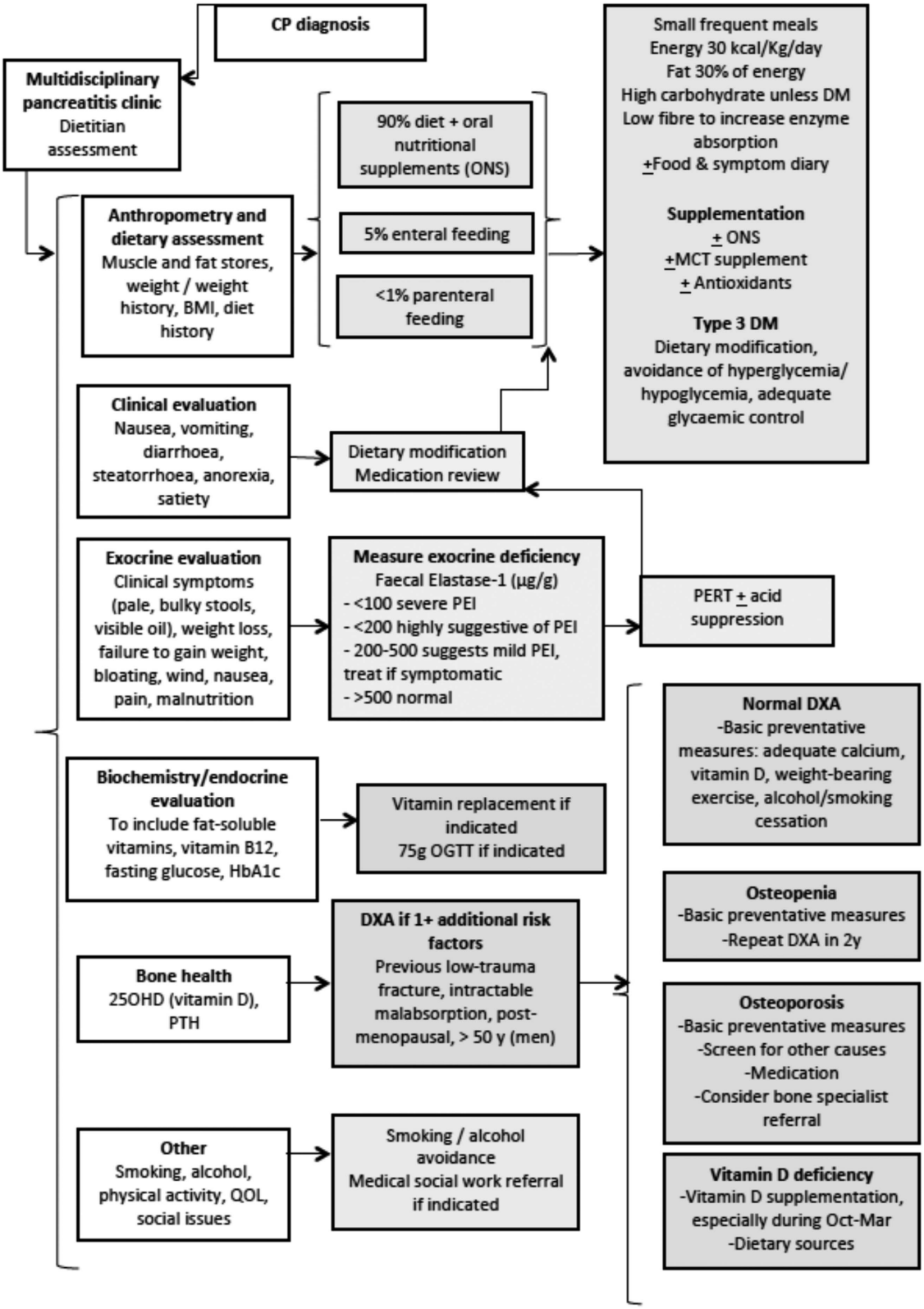

Figure 1. The nutritional assessment of patients with chronic pancreatitis. Adapted with permission from Duggan *et al.*[39] BMI, body mass index; CP, chronic pancreatitis; 25OHD, 25 hydroxyvitamin D; PTH, parathyroid hormone; QOL, quality of life; OGTT, oral glucose tolerance test; DXA, dual X-ray absorptiometry; DM, diabetes mellitus.

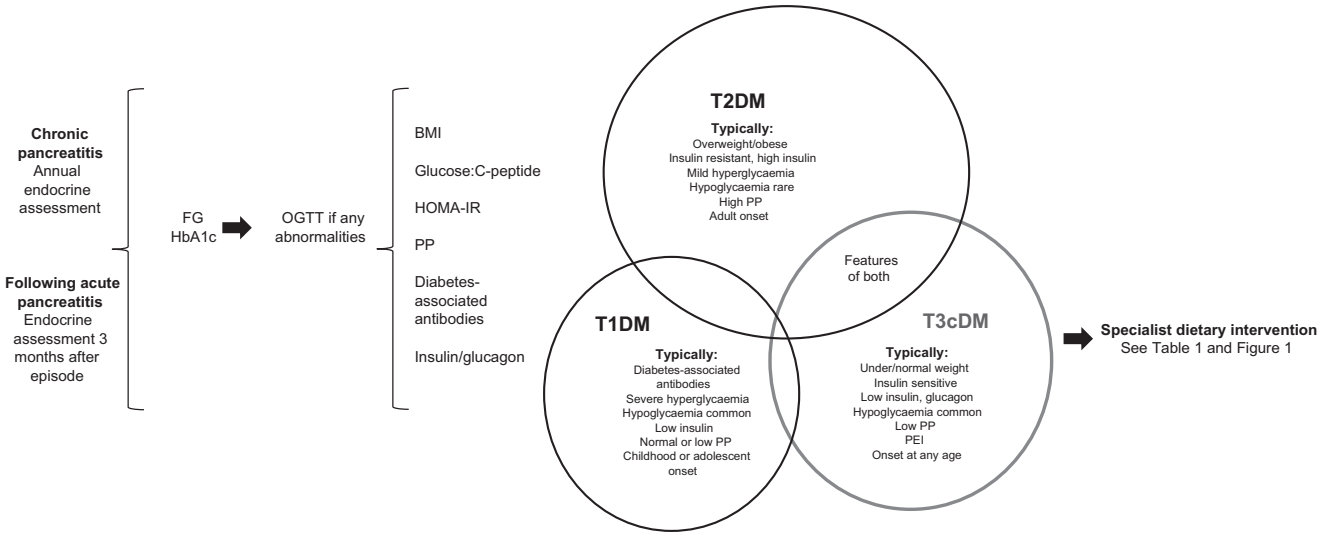

Figure 2. Suggested endocrine follow-up and assessment of patients with pancreatitis. FG, fasting glucose; HbA1c, glycated haemoglobin; OGTT, oral glucose tolerance test; PEI, pancreatic exocrine insufficiency; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

begins to properly absorb nutrients, including carbohydrate.[38] Patients may also increase dietary intake following PERT therapy, as symptoms diminish, thereby potentially affecting blood sugar control.

Table 1 shows suggested priorities and management goals for the nutritional management of T3cDM in chronic pancreatitis.[33] Naturally, T3cDM should not be considered in isolation, but endocrine assessment should be part of the overall clinical and nutritional work-up of patients with chronic pancreatitis, which should include anthropometric, biochemical, dietary and exocrine function assessment, along with assessments of bone health, and counselling for alcohol and smoking cessation if appropriate. Patients with chronic pancreatitis are nutritionally complex with heterogeneous needs necessitating regular, patient-specific nutritional assessment and monitoring. Figure 1 provides a detailed schematic for the nutritional management of patients with chronic pancreatitis.[33,39]

ACUTE PANCREATITIS

In a systematic review of 24 studies comprising 1102 subjects after the first attack of acute pancreatitis, almost 4 in 10 patients had either prediabetes or diabetes (25% had frank diabetes).[40] Of the patients with diabetes, the majority (70%) required permanent insulin therapy, with a two-fold risk of requiring insulin at 60 months following acute pancreatitis compared with 12 months. Limitations of the systematic review included failure of many of the primary studies to account for obesity or family history and to measure other endocrine indices (such as insulin resistance, insulin secretion and glucagon secretion). Whether or not patients have true T3cDM or elements of type 2 diabetes has not been properly investigated. Nevertheless, the fact remains that patients who have had acute pancreatitis have a considerable risk of developing diabetes, with an even higher risk after 5 years, and therefore endocrine evaluation should be a priority for those who have survived an episode of severe acute pancreatitis. It has been suggested that endocrine function should be evaluated for all patients 3 months following an episode of acute pancreatitis by the measurement of both fasting and post-prandial blood glucose levels, and possibly by measuring HbA1c.[41]

SUMMARY

T3cDM is a diabetes subgroup relating to diseases of the exocrine pancreas, such as chronic pancreatitis. However, there is poor awareness of this condition, and patients may therefore be misclassified, usually as T2DM. The nutritional management of T3cDM should include regular dietary assessment and monitoring to prevent hypoglycaemia, reduce hyperglycaemia, prevent malnutrition, treat PEI and reduce the risk of diabetes-related complications. Figure 2 illustrates the suggested assessment and follow-up for patients with pancreatitis to facilitate the timely diagnosis and treatment of T3cDM.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

SND conceived the idea, performed the literature searches and wrote the manuscript. NE, LK, OMG and JG assisted in writing the manuscript and critically evaluated the manuscript. KCC assisted in writing the manuscript, critically evaluated the manuscript and is a guarantor of the manuscript.

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