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Pancreatogenic Type 3c Diabetes: Underestimated, Underappreciated and Poorly Managed

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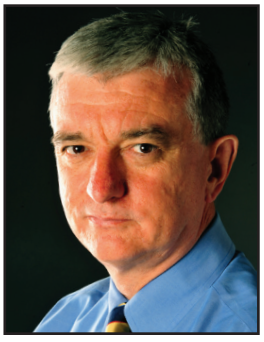

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Type 3c diabetes, also known as pancreatogenic diabetes, refers to diabetes resulting from pancreatic disease, including pancreatitis, cystic fibrosis and pancreatic cancer. It is difficult to diagnose, and for many, management is challenging due to erratic swings from hypoglycemia to hyperglycemia caused by metabolic abnormalities due to pancreatic tissue damage. This review aims to describe the disease along with its characteristics, diagnosis, complications, and management.

CLINICAL CASE 1

A 42 year old male with an eight-year history of alcohol-induced chronic pancreatitis was admitted from the ER. His current weight was 61Kg as opposed to his usual weight of 67Kg; his appearance was cachectic. He reported abdominal pain, intermittent diarrhea/steatorrhea along with periods of constipation, cramping, flatulence and poor appetite. He was not compliant with prescribed pancreatic enzyme replacement therapy (PERT), was still abusing alcohol, and was a heavy smoker for many years. He took opiates for relief of chronic, constant abdominal pain. His dietary intake was minimal over the past week and poor for several years. He was admitted and re-educated regarding adequate dietary intake, prescribed oral nutritional supplements, and counselled on adequate and appropriate usage of PERT. Blood work revealed low levels of serum vitamins (25 OHD, vitamin E and vitamin A), normal fasting glucose and HbA1c. He was discharged after 3 days once he was established on adequate oral diet, micronutrient supplementation, PERT, and his pain medication had been adjusted. He was readmitted three weeks later with dehydration, fatigue, excess thirst and blurred vision. Fasting glucose was measured and was elevated at 250 mg/dl (13.9 mmol/L), therefore new diabetes mellitus (DM) was diagnosed. A referral was made to the endocrinology service for further evaluation.

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CLINICAL CASE 2

A 37 year old female with a five-year history of type 2 diabetes mellitus (T2DM) presented to the gastroenterology outpatient clinic complaining of a 6

month history of diarrhea (3-4 times per day), flatulence and bloating. She had taken anti-diarrheal medication with limited effect. She reported that the diarrhea tended to occur post-prandially, and was worse with larger, 'richer' meals. She reported that she could see visible oil in the toilet pan after defecating, requiring several flushes. She also had a history of three episodes of hypertriglyceridemia-induced acute pancreatitis. On one occasion the acute pancreatitis had been deemed 'severe' and she was hospitalized for several weeks, including one week in the critical care unit requiring enteral feeding. She was 88Kg (BMI 30.4 Kg/M2). Given her history of acute pancreatitis, and the oily nature of her stools, pancreatic exocrine insufficiency (PEI) was suspected and a fecal elastase-1 test ordered. Results showed faecal elastase-1 of 95µg /g (indicating severe PEI). She was referred to a pancreatologist for further workup and pancreatic imaging.

INTRODUCTION

According to the American Diabetes Association (ADA), there are four DM subgroups. Most are familiar with type 1 diabetes (T1DM), an immune-mediated condition associated with beta-cell destruction leading to absolute insulin deficiency. T2DM is well recognized as a spectrum involving varying degrees of peripheral insulin resistance and beta cell dysfunction. Type 4 DM refers to gestational or pregnancy-related diabetes.[1] This review will focus on Type 3 DM, categorized by the ADA as 'other specific types of diabetes'. In particular we will focus on type 3c diabetes (T3cDM), which refers to DM arising from diseases of the exocrine pancreas. T3cDM is also referred to as pancreatogenic or apancreatic DM. A study from Europe on the reclassification of nearly 2,000 patients with DM reported that 8% of patients should have been diagnosed with T3cDM, rather than T1DM or more usually, T2DM.[2] Three-quarters of the patients reclassified as having T3cDM had chronic pancreatitis, while the rest had haemochromotosis, cystic fibrosis, or were pancreatic cancer patients. Therefore, this study showed that T3cDM was reasonably common. Several clinical and biochemical indices distinguish T3cDM from T1DM and T2DM (see Table 1). Due to its association with pancreatic disease, patients are more likely to be undernourished or have nutrient deficiency.[3] Pancreatic exocrine insufficiency (PEI) will also be a feature resulting in fat malabsorption. The management of patients with T3cDM is challenging due to a number of metabolic features (especially low glycogen stores due to malnutrition making counter-regulation difficult, normal glycated hemoglobin due to long standing poor nutrient absorption, then sudden nutrient utilization once PERT initiated, exaggerated response to smaller doses of insulin to name a few) resulting in severe swings in glucose levels from hypoglycemia to hyperglycemia, which in its most severe form is termed, 'brittle diabetes'.

PREVALENCE OF T3cDM

While the study from Germany by Ewald and colleagues found that 8% of all diabetes patients had T3cDM, most of which had chronic pancreatitis, the occurrence of T3cDM in this disease actually ranges widely from 5% to more than 80%. It is higher in patients who have undergone surgical resection, especially of the distal pancreas.[4] Smoking,[5-7] longer duration of disease,[4,8] and the presence of pancreatic calcifications[4,9,10] increases the likelihood of developing DM in chronic pancreatitis. In general, it is thought that T3cDM is vastly underestimated. With the increased rates of pancreatic surgery and pancreatectomy, the increasingly higher survival of cystic fibrosis patients, and the increasing prevalence of chronic pancreatitis world-wide, T3cDM is of growing importance.[11]

DIAGNOSIS AND DIFFERENTIATION OF T3cDM

Initial diagnosis of T3cDM (as for types 1 and 2), includes measurement of fasting glucose and glycated hemoglobin (HbA1c or A1c), repeated annually for those with pancreatitis. Equivocal results should arguably be investigated further by means of an oral glucose tolerance test.[12] The ADA guidelines state that fasting plasma glucose of >126 mg/dl (>7mmol/L) or HbA1c of >48 mmol/mol (6.5%) are diagnostic of DM, while a fasting glucose of 100-125 mg/dl (5.5-6.9mml/L) or HbA1c of 39-46 mmol/mol (5.7-6.4%) are indicative of prediabetes.[1,13] However, differentiating T3cDM from T1DM and T2DM is not always straightforward.[14] Destruction of the islet cells by pancreatic inflammation differs from that in T1DM as there is also a loss of glucagon and pancreatic polypeptide (PP) from the islet alpha cells and PP cells (as well as the loss of insulin from the islet beta-cells). Additionally, nutrient maldigestion and malabsorption lead to impaired incretin secretion and therefore diminished release from the remaining beta cells. Although circulating insulin levels are known to

be low in T3cDM, along with a compensatory increase in peripheral insulin sensitivity, there is a decrease in hepatic insulin sensitivity (and unsuppressed hepatic glucose production), which drives hyperglycemia (see Table 1). The impairment of hepatic insulin sensitivity and persistent hepatic glucose production is associated with the reduction in pancreatic PP secretion.[11] Therefore, the DM associated with pancreatic disease is erratic in nature, characterized by significant swings in blood glucose from hypoglycemia to hyperglycemia in a manner which is difficult to control.

Ewald and Hardt[14] devised diagnostic guidelines for T3cDM, providing useful major and minor criteria which suggest a diagnosis of T3cDM. Major criteria which must be present include:

1. Pancreatic exocrine insufficiency
2. Pathological pancreatic imaging
3. Absence of T1DM-associated auto-antibodies.

The minor criteria were absent PP secretion, impaired incretin secretion, absence of excessive insulin resistance, impaired beta-cell function, and low serum levels of fat-soluble vitamins.

Assessment and monitoring of patients with pancreatic disease should include body mass index, diabetes-associated antibodies (to out rule T1DM), and glucose to c-peptide ratio which estimates beta-cell area.[12] Insulin resistance is measureable by the homeostasis model assessment, which estimates steady state beta-cell function and insulin sensitivity as percentages of a normal reference range. This is calculated based on fasting plasma glucose and insulin values. Unlike T2DM patients, those with T3cDM will not normally have excess insulin resistance. The absence of (or reduced) PP secretion following ingestion of glucose or a mixed meal may also be indicative of T3cDM.[14] However, these guides require the measurement of incretin, PP and c-peptide levels, among others, which in everyday practice is unlikely to occur. Table 1 compares the clinical and laboratory characteristics of T3cDM with that of T1DM and T2DM, which is an expansion of earlier versions by Slezak and Andersen[15] and Cui and Andersen.[11]

While T3cDM has features which overlap with both T1DM and T2DM, it is clinically and metabolically distinct from both, having unique characteristics and specific management priorities requiring tailored therapy. The additional complication of nutrient malabsorption, and frequently poor oral diet (to avoid symptoms), including chronic pain; smoking and/or alcoholism), renders the T3cDM patient at high risk of undernutrition and critical hypoglycemia. In clinical case 1, the patient did not present with gross steatorrhea as one might expect in advanced chronic pancreatitis (but remember one has to eat fat to malabsorb it — often intake can be so poor, this is another reason why it is missed), therefore it might be perceived that the small amounts of PERT taken was adequate to counteract PEI. However, once normal diet resumed and PERT dosage/administration were optimized (allowing optimal absorption of nutrients including carbohydrate), there was an 'unmasking' of his DM. In patients who already have a diagnosis of DM, there may be a profound worsening of hyperglycemia. Where patients take opiates due to chronic pain, constipation may be a surprising feature of chronic pancreatitis, leading the clinician to believe that PERT is adequate or unnecessary, contributing to undernutrition and nutrient deficiency. In clinical case 2, our patient with DM had undiagnosed PEI demonstrating that altered pancreatic function should be considered in diabetic patients with intractable gastro-intestinal symptoms, particularly those with a history of pancreatic disease.

COMPLICATIONS OF T3cDM

Retinopathy, renal dysfunction, neuropathy and microangiopathic complications appear to occur as frequently in T3cDM as in T1DM and T2DM.[16-19] It is thought that macrovascular complications occur less frequently due to chronic malabsorption and commonly-occurring undernutrition, however research and long-term studies are lacking and the risks are incompletely understood.

PHARMACOLOGICAL TREATMENT OF T3cDM

There are few, if any, studies on the pharmacological treatment of T3cDM. In fact, patients with T3cDM were specifically excluded from many large-scale DM studies due to their unique, eccentric clinical and metabolic characteristics. In chronic pancreatitis, for those with severe undernutrition, insulin is usually required to control blood glucose levels. Notably, Cui et al. have cautioned against using insulin in chronic pancreatitis (calling it a 'pre-malignant condition').[11] It should be noted that the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial,[20] which included

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Table 1. Comparing and Contrasting the Characteristics of Types 1, 2 and 3c Diabetes*

Characteristic	Type 1 Diabetes
Hyperglycemia	Severe
Hypoglycemia	Common
Ketoacidosis	Common
Diabetes-associated antibodies	Yes
Insulin Levels	Low
Glucagon Levels	Normal or High
Peripheral Insulin Sensitivity	Normal or Increased
Hepatic Insulin Sensitivity	Normal
Pancreatic Polypeptide Levels	Normal or Low (may be low or absent in those with severe autonomic neuropathy[27])
Incretin Secretion • Gastric Inhibitory Polypeptide (GIP) Levels • Glucagon-like Peptide-1 (GLP-1) Levels	 Normal or Low Normal
Age of Onset	Childhood or Adolescence
Overweight/Obese	Rare
Undernutrition	Uncommon
Nutrient Deficiency	Rare
Bone Mineral Density / Risk of Fracture	Risk of low bone mineral density and higher fracture risk, especially at the hip[32]
Risk of Pancreatic Cancer	No higher risk[29]

**Based on earlier tables by Slezak and Andersen[15] (permission obtained) and Cui YF and Andersen DK[11]*

Type 2 Diabetes	Type 3c Pancreatogenic Diabetes
Usually Mild	Mild, or severe in 'brittle diabetes' • Due to unsuppressed hepatic glucose production • Exaggerated (peripheral) sensitivity to insulin
Rare	Common and may be severe • Deficiency in glucagon secretion o Impaired activation of gluconeogenesis • Hepatic insulin sensitivity is reduced, due to deficiency in polypeptide secretion o Exogenous insulin delivery exaggerates this • Peripheral sensitivity to insulin enhanced from relative hyperinsulinemia & reduced counter-regulatory hormone release (glucagon) • Poor dietary intake due to pain, smoking, alcohol or symptom avoidance • PEI with malabsorption • Persistent alcohol intake in some
Rare	Rare
Rare	No
High	Low
Normal or High	Low
Decreased	Increased
Normal or Decreased	Decreased
High (may be decreased in those with severe autonomic neuroapthy[27])	Low
	Incretin secretion is impaired in the setting of maldigestion, hence diminished insulin release from remaining beta-cells
Normal or High Low or normal[16] (may increase with metformin therapy or with PERT[28])	Low Normal or High[14]
Mainly in Adulthood	Any (chronic pancreatitis usually presents in adulthood)
Common	Uncommon. However, patients with chronic pancreatitis may be overweight or obese, but have muscle depletion compared to matched controls[3]
Rare	Common[25,26,29]
Rare	Deficiency of fat-soluble vitamins is common in chronic pancreatitis due to PEI and poor diet[3,30,31]
May have low bone mineral density, although may also have increased fracture risk despite normal/high bone mineral density (could be related to falling risk due to complications such as poor eyesight, neuropathy)[32]	Depending on the type of pancreatic disease, the risk of low bone mineral density is substantial. In chronic pancreatitis, 65% of patients have either osteoporosis or osteopenia[33], and there is a high risk of atraumatic fracture compared to controls[34,35]
Twofold risk of developing pancreatic cancer[36]	5% of patients with chronic pancreatitis will develop pancreatic cancer over a 20-year period Risk of pancreatic cancer higher for patients with both chronic pancreatitis and diabetes, than for those with chronic pancreatitis alone (although diabetes could be a manifestation of pancreatic cancer rather than a risk factor)[37]

Table 2. Suggested Principles of Management/Management Strategies for Type 3c Diabetes in Chronic Pancreatitis

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

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patients with impaired fasting glucose, impaired glucose tolerance and T2DM, showed that there was no increase in incident cancers for those on insulin glargine *versus* standard care. The risk of developing pancreatic cancer for those with chronic pancreatitis is higher than the general population, and for those with T2DM, the risk of developing pancreatic cancer is twice that of the general population. However, those with T2DM are at a higher risk for many cancer types, so the risk is not confined to pancreatic cancer alone.[21] In fact, many will require insulin to control rampant hyperglycemia, and its anabolic effects are welcome in those with undernutrition. For those with more mild hyperglycemia and concomitant insulin resistance, metformin could be used if not contraindicated, although it may cause gastrointestinal side-effects such as nausea and diarrhea, unwelcome additions in pancreatic disease. Even where insulin therapy is required, metformin and other oral hypoglycemic agents could be used to reduce the requirement for large amounts of insulin.[22]

NUTRITIONAL MANAGEMENT OF T3cDM

The PancreasFest Working Group[23] were the first to provide a diagnostic and management framework for T3cDM in chronic pancreatitis. They recommended that patients with T3cDM should be treated with specifically-tailored medical nutrition, and that the primary goals are to prevent or treat malnutrition, control symptoms of the steatorrhea, and to minimize meal-induced hyperglycemia. Cui and Andersen stated that initial therapy should begin with correction of lifestyle factors which contribute to hyperglycemia and malignancy, including reinforcing weight loss for the obese, daily exercise, and limited carbohydrate, along with recommending abstinence of alcohol and smoking cessation at every medical visit.[11]

A recent review by Duggan et al. aimed to provide detailed dietary guidelines.[12] In the first instance, dietary management should prioritize the prevention

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Table 3. Suggested Self-Monitoring Regimen for Blood Glucose Testing in T3cDM*

Minimum 6-10 blood glucose testing occasions per day:

- Prior to all meals and snacks
- Occasionally post-prandially
- Before bed
- After physical activity
- In the presence of suspected hypoglycemic symptoms
- After treating for hypoglycemia until normoglycemia is maintained
- Before critical tasks e.g. driving, swimming, using dangerous equipment, etc.

**Based on ADA self-monitoring blood glucose testing for T1DM and T2DM patients on intensive insulin regimens[38]*

of hypoglycemic events and the provision of education regarding hypoglycemia symptoms and treatment (Table 2). A regular meal plan with specified, controlled amounts of starchy carbohydrate should be provided. Blood glucose should be monitored regularly (Table 3), with self-monitoring recommended especially for those on intensive insulin regimens. This is based on the ADA recommendations for T1DM and T2DM patients on intensive insulin regimens. The ADA did not provide a guide specifically for T3cDM, but given the risks of hypoglycemia and the difficulties in management, such a monitoring regimen could be implemented if tolerated by the patient. According to the ADA, such intensive monitoring regimes are probably not required for those on basal insulin plans, or for those taking oral hypoglycemic agents.

Those with 'brittle' DM in particular should maintain a record of blood glucose values, dietary intake, physical activity, and PERT usage to aid in dietary review and assessment.[12] Continuous Glucose Monitoring (CGM) may have an important role in patients with brittle diabetes. The recently Food and Drug Administration (FDA)-approved DEXCOM (www.dexcom.com; San Diego, CA) G5 mobile CGM system is externally-worn glucose sensor which reports values every 5 minutes. This allows for the prediction of imminent hypo- or hyperglycemia, and reduces the requirement for multiple fingerstick blood glucose testing. The DEXCOM system uses algorithmic signal processing to convert raw electrochemical blood glucose values. Therefore the CGM system may allow for a reduction in HbA1c, without an increased risk of hypoglycemia.[24]

Alcohol, which will exacerbate hypoglycemia, should be avoided or minimized. The second priority is to reduce the frequency and extent of hyperglycemic events to minimize the risk of diabetes-associated complications. This includes minimizing simple sugar sources, especially in liquid form, and following a low-glycemic diet, where feasible. 'Diabetic' foods, which are expensive and may have a laxative effect in large quantities due to sorbitol (and other sugar alcohols) content, are generally not recommended. Adequate PERT, taken appropriately, is crucial to ensure nutrient absorption. Education around malabsorptive symptoms and dose titration should be provided.[12] Management of T3cDM in pancreatic disease represents just one of the challenges in the nutritional management of this complex patient group. In both chronic pancreatitis and cystic fibrosis, regular anthropometric assessment, biochemical workup, and evaluation of bone health should accompany endocrine, exocrine and dietary evaluation.[25,26] The ADA recommended that an individualized medical nutrition therapy program be established by a registered dietitian; specifically they recommended that an individualized eating plan be established. This recommendation, again, was for patients with T1DM and T2DM, but would also be vital in T3cDM.

CONCLUSION

In summary, T3cDM is a clinically important disease, which has to date been underestimated and underappreciated, and thus, tends to be poorly managed. As yet, there remain many research gaps regarding its diagnosis and management. Close, careful

monitoring and follow-up is essential to ensure good glycemic control, optimization of intestinal absorption and nutritional status, as well as to account for the complex array of factors contributing to this challenging condition. ■

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2014;37 Suppl 1:S81-90.
2. Ewald N, Kaufmann C, Raspe A, et al. Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c). *Diabetes Metab Res Rev.* 2012;28(4):338-342.
3. Duggan SN, Smyth ND, O'Sullivan M, et al. The prevalence of malnutrition and fat-soluble vitamin deficiencies in chronic pancreatitis. *Nutr Clin Pract.* 2014;29(3):348-354.
4. Malka D, Hammel P, Sauvanet A, et al. Risk factors for diabetes mellitus in chronic pancreatitis. Gastroenterology. 2000;119(5):1324-32.
5. Wang W, Guo Y, Liao Z, et al. Occurrence of and risk factors for diabetes mellitus in Chinese patients with chronic pancreatitis. *Pancreas*. 2011;40(2):206-212.
6. Maisonneuve P, Lowenfels AB, Mullhaupt B, et al. Cigarette smoking accelerates progression of alcoholic chronic pancreatitis. *Gut.* 2005;54(4):510-514.
7. Maisonneuve P, Frulloni L, Mullhaupt B, et al. Impact of smoking on patients with idiopathic chronic pancreatitis. *Pancreas.* 2006;33(2):163-168.
8. Ito T, Otsuki M, Igarashi H, et al. Epidemiological study of pancreatic diabetes in Japan in 2005: a nationwide study. *Pancreas.* 2010;39(6):829-835.
9. Rajesh G, Veena AB, Menon S, et al. Clinical profile of early-onset and late-onset idiopathic chronic pancreatitis in South India. *Indian J Gastroenterol*. 2014;33(3):231-6.
10. Bhasin DK, Singh G, Rana SS, et al. Clinical profile of idiopathic chronic pancreatitis in North India. *Clin Gastroenterol Hepatol*. 2009;7(5):594-9.
11. Cui Y, Andersen DK. Pancreatogenic diabetes: special considerations for management. *Pancreatology.* 2011;11(3):279-294.
12. Duggan SN, Ewald N, Kelleher L, et al. The nutritional management of type 3c (pancreatogenic) diabetes in chronic pancreatitis. *Eur J Clin Nutr*. 2016 Jul 13.
13. American Diabetes Association. 2. Classification and Diagnosis of Diabetes. *Diabetes Care.* 2016;39 Suppl 1:S13-22.
14. Ewald N, Hardt PD. Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. *World J Gastroenterol.* 2013;19(42):7276-7281.
15. Slezak LA, Andersen DK. Pancreatic resection: effects on glucose metabolism. *World J Surg.* 2001;25(4):452-460.
16. Levitt NS, Adams G, Salmon J, et al. The prevalence and severity of microvascular complications in pancreatic diabetes and IDDM. *Diabetes Care*. 1995;18(7):971-974
17. Gasiorowska A, Czupryniak L, Malecka-Panas E, et al. [Microvascular complications in pancreatic diabetes]. *Pol Arch Med Wewn*. 2001;105(6):469-474
18. Gullo L, Parenti M, Monti L, et al. Diabetic retinoapthy in chronic pancreatitis. *Gastroenterology*. 1990;98(6):1577-1581
19. Ito T, Otsuki M, Igarashi H. Epidemiological study of pancreatic diabetes in Japan in 2005: a nationwide study. *Pancreas*. 2010;39(6):829-835
20. Gerstein HC, Bosch J, Dagenais GR, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med*. 2012;367(4):319-328
21. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: A consensus report. Diabetes Care. 2010;33(7):1674-1685
22. Meier JJ, Nauck MA. Is the diminished incretin effect in type 2 diabetes just an epi-phenomenon of impaired beta-cell function? *Diabetes.* 2010;59(5):1117-1125.
23. Rickels MR, Bellin M, Toledo FG, et al. Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: recommendations from PancreasFest 2012. *Pancreatology.* 2013;13(4):336-342.
24. Joubert M, Resnik Y. Personal Continuos Glucose Monitoring (CGM) in diabetes management: review of the literature and implementation for practical use. Diabetes Res Clin Pract. 2012;96(3):294-305
25. Duggan S, O'Sullivan M, Feehan S, et al. Nutrition treatment of deficiency and malnutrition in chronic pancreatitis: a review. *Nutr Clin Pract.* 2010;25(4):362-370.
26 Duggan SN, Conlon KC. A practical guide to the nutritional management of chronic pancreatitis. *Practical Gastroenterol.* 2013;118:24-32.
27. Bolinder J, Sjoberg S, Persson A, et al. Autonomic neuropathy is associated with impaired pancreatic polypeptide and neuropeptide Y responses to insulin-induced hypoglycaemia in Type I diabetic patients. *Diabetologia.* 2002;45(7):1043-1044.
28. Knop FK, Vilsboll T, Larsen S, et al. Increased postprandial responses of GLP-1 and GIP in patients with chronic pancreatitis and steatorrhea following pancreatic enzyme substitution. *Am J Physiol Endocrinol Metab.* 2007;292(1):E324-330.
29. Lankisch PG. Chronic pancreatitis. *Curr Opin Gastroenterol.* 2007;23(5):502-507.
30. Sikkens EC, Cahen DL, Koch AD, et al. The prevalence of fat-soluble vitamin deficiencies and a decreased bone mass in patients with chronic pancreatitis. *Pancreatology.* 2013;13(3):238-242.
31. Lindkvist B, Dominguez-Munoz JE, Luaces-Regueira M, et al. Serum nutritional markers for prediction of pancreatic exocrine insufficiency in chronic pancreatitis. *Pancreatology.* 2012;12(4):305-310.
32. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes--a meta-analysis. *Osteoporos Int.* 2007;18(4):427-444.
33. Duggan SN, Smyth ND, Murphy A, et al. High prevalence of osteoporosis in patients with chronic pancreatitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2014;12(2):219-228.
34. Bang UC, Benfield T, Bendtsen F, et al. The risk of fractures among patients with cirrhosis or chronic pancreatitis. *Clin Gastroenterol Hepatol.* 2014;12(2):320-326.
35. Tignor AS, Wu BU, Whitlock TL, et al. High prevalence of low-trauma fracture in chronic pancreatitis. *Amer J Gastroenterol.* 2010;105(12):2680-2686.
36. Muniraj T, Chari ST. Diabetes and pancreatic cancer. *Minerva Gastroenterol Dietol.* 2012;58(4):331-345.
37. Dhar P, Kalghatgi S, Saraf V. Pancreatic cancer in chronic pancreatitis. *Indian J Surg Oncol.* 2015;6(1):57-62.
38. American Diabetes Association. 5. Glycemic Targets. *Diabetes Care.* 2016;39 Suppl 1:S39-46.