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Mini Review

Type 3 Diabetes Mellitus: Brief Review

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Abstract

Diabetes mellitus, disease of endocrine dysfunction of pancreas has been found to have simultaneous exocrine insufficiency also by numerous researchers. Type 3 Diabetes Mellitus (T3cDM) also referred as pancreatogenic diabetes has been observed to develop among patients of chronic pancreatitis and other pancreatic disorders. During early course of the disease, glucose intolerance may be in mild form mainly due to obstruction of islet cells by pancreatic inflammation, but with the progression of the disease it present as brittle diabetes, which is characterized by marked glycemic swings from hyperglycemia to hypoglycemia. Key challenging issue about T3cDM is its diagnosis as frequently it is misclassified as Type 1 or 2 DM. Very often in clinical practice, T3cDM remains neglected diagnosis because of standard guidelines for its diagnosis, overlapping clinical picture of T1DM, T2DM associated with exocrine pancreatic dysfunction. Managing patients with T3cDM is challenging task for the physicians due to number of metabolic dysfunctions and poor nutritional status. So early measures are necessary to diagnose diabetes mellitus among chronic pancreatitis patients. Along with glycemic control, correction of pancreatic exocrine insufficiency is very important aspect while treating T3cDM cases.

Keywords: Typ3c Diabetes mellitus; Chronic pancreatitis; Exocrine function

Introduction

Diabetes secondary to pancreatic diseases is frequently referred as pancreatogenic diabetes or Type 3 Diabetes Mellitus (T3cDM). It is also classified as pancreatogenic, pancreoprive, apancreatic or secondary diabetes mellitus by American Diabetes Association and world health organization. Several exocrine pancreatic disorders including benign and malignant conditions like acute, relapsing and chronic pancreatitis have been identified as underlying causes for development of T3cDM. Among these, the most common cause is chronic pancreatitis (78.5% of T3cDM cases) followed by carcinoma of pancreas (8% of T3cDM). Other etiological factors are hemochromatosis, cystic fibrosis, fibrocalculous pancreatitis, pancreatectomy, agenesis, trauma and cancer of pancreas. T3cDM was considered as rare clinical entity [1]. But now it is found commonly with reported prevalence of 5-10% among all diabetics [2]. At one of the institute of gastroenterology, clinicians observed that 38% of chronic pancreatitis develop diabetes within 1-2 years of CP suggesting early beta cell dysfunction in CP [3]. Diabetes mellitus, disease of endocrine dysfunction of pancreas has been found to have simultaneous exocrine insufficiency also by numerous researchers.

Clinical Profile and Etiopathology of T3cDM

Most of the patients present with history of chronic pancreatitis with abdominal pain, symptoms of steatorrhea, maldigestion, glucose intolerance and manifestations of the deficiency of several nutrients. During early course of the disease, glucose intolerance may be in mild form, but with the progression of the disease it present as brittle diabetes, which is characterized by marked glycemic swings from hyperglycemia to hypoglycemia [4]. If a newly diagnosed patient of DM present with unusual clinical picture and gastrointestinal symptoms, clinicians should think about possibility of T3cDM and plan further management accordingly to confirm the diagnosis and initiate the treatment.

T3cDM is a distinct clinical condition from T1DM and T2DM because it occurs due to chronic inflammatory environment and increased concentration of cytokines within the pancreatic parenchyma and result in high incidence of associated pancreatic cancer. With progression of chronic pancreatitis, the extensive fibrosis of the exocrine pancreas slowly destroys the islet pancreatic tissue. Etiopathology of T3cDM is very complex and multifactorial. Hepatic insulin resistance with persistent gluconeogenesis and deficient pancreatic polypeptide response has been observed in T3cDM patients [5]. Destruction of the islet cells due to pancreatic inflammation in T3cDM result in loss of glucagon and pancreatic polypeptides from islet alpha cells [6]. In case of CP, glucose intolerance and diabetes develops mainly due to obstruction of islet cells by pancreatic inflammation. Also impaired digestion of nutrients hampers secretion of incretin and so reduced insulin secretion from remaining beta cells [7].

Diagnosis of T3cDM

Key challenging issue about T3cDM is its diagnosis. Frequently it is misclassified as T1DM or T2DM. Ewald N et al reclassified 8% of patients as T3cDM rather than T1DM or T2DM among a cohort of 2000 diabetic patients. Chronic pancreatitis was present among three quarters of T3cDM patients while remaining had cystic fibrosis, hemochromatosis or pancreatic cancer [8]. Numerous unique clinical and laboratory markers help to differentiate T3cDM from other types of DM. For diagnosis of T3cDM, following criteria has been suggested- Major criteria- presence of exocrine insufficiency (monoclonal fecal elastase-1 test or direct function tests), pathological pancreatic imaging (endoscopic ultrasound, computerized tomography, magnetic

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resonance imaging) and absence of T1DM associated autoimmune markers. Minor criteria- impaired beta cell function (HOMA-B, C-peptide / glucagon ratio, no excessive insulin resistance, impaired secretion of incretin, decreased levels of fat soluble vitamins (A, D, E ,K) [1]. Very often in clinical practice, T3cDM remains neglected diagnosis because of standard guidelines for its diagnosis, overlapping clinical picture of T1DM, T2DM associated with exocrine pancreatic dysfunction. Hepatic insulin resistance due to deficiencies of insulin and pancreatic polypeptides is a characteristic of T3cDM [9]. Worldwide, around 10% of total diabetics have been diagnosed for chronic pancreatitis characterized by progressive fibrosis, irreversible exocrine and early onset endocrine dysfunction of pancreas. Patients of acute and or chronic pancreatitis may develop T1DM or T2DM independent of their pancreatic exocrine failure [10]. In addition to this, diabetic patients are at high risk for developing acute and or chronic pancreatitis and pancreatic cancer [11]. Hence differentiation of T3cDM from T1DM and T2DM is difficult. Fecal elastase 1 test can be used for screening pancreatic exocrine function. Absence of pancreatic polypeptide response to mixed-nutrient ingestion can help in differentiating T3cDM from T2DM [12].

Managing patients with T3cDM is challenging task for the physicians due to number of metabolic dysfunctions and poor nutritional status. So early measures are necessary to diagnose diabetes mellitus among CP patients. They should be screened regularly with fasting blood glucose, glycated hemoglobin assay and glucose tolerance tests if required. Also non-diabetic CP patients should be assessed for the presence of beta cell dysfunction before development of overt hyperglycemia and clinical diabetes. Sasikala M et al reported extended glucose tolerance curve among 30% of non-diabetic CP patients. They also observed that 38% of CP patients develop diabetes early, just within 1-2 years of diagnosis of CP [3]. Complications of T3cDM include microvascular complications frequently like retinopathy, nephropathy, neuropathy [13].

Management of T3cDM

Clinical course of T3cDM is very complex because of nutritional deficiencies due to associated exocrine insufficiencies. Because of loss of glucagon response to hypoglycemia, malabsorption of carbohydrates and inconsistent eating due to pain, nausea or chronic alcoholism, glycemic control is very difficult among patients with T3cDM. Planning diet with regular small meals with starchy carbohydrates, avoiding high glycemic index food alcohol and smoking help to control the glycemic status. Severe swings from hypoglycemic state to hyperglycemia are observed due to number of metabolic features like low glycogen stores, poor absorption of nutrients and then sudden utilization of nutrients on supplementation of pancreatic enzymes [6]. Prevention of hypoglycemic episodes is very important while managing T3cDM patients. Standard guidelines for management of T3cDM are not available at present. But same pharmacological therapeutic agents used for treatment of T2DM are used typically used for the treatment of T3DM. Insulin and insulin segretagogue carries the risk of development of pancreatic cancer. Metformin reduces such risk. It is a first drug of choice, but many times not tolerated by T3cDM patients because of side effects of gastrointestinal complaints and weight reduction. Incretin based therapies also enhance secretion of insulin, but they also are associated with gastrointestinal complaints [14]. Many patients need insulin therapy because of progressive nature of chronic pancreatitis. For such patients, dose of insulin should be administered as per the guidelines for Type 1 DM patients. Brittle diabetes should be monitored with continuous Glucose monitoring to avoid fluctuations in glycemic status.

Along with glycemic control, correction of pancreatic exocrine insufficiency is very important aspect while treating T3cDM cases. Addition of proper pancreatic enzymes help to prevent secondary nutritional and metabolic complication of T3cDM [9]. Absorption of fat-soluble vitamins is also hampered. Estimation of levels vitamin D and its supplementation is needed to prevent osteoporosis [15]. Exocrine insufficiency in chronic pancreatitis is associated with a functional impairment of incretin system; which can be normalized by supplementation of pancreatic enzymes [16]. Adequate supplementation of pancreatic enzymes also helps to control symptoms of steatorrhea. Therapeutic lifestyle change also should be included as a part of management of T3cDM for better prognosis.

Conclusion

T3cDM refers to DM arising from diseases of exocrine pancreas with unique pattern of metabolic and hormonal characteristics. It occurs due to inherited or acquired pancreatic disease or resection and is associated with high incidence of pancreatic cancer. Additional malnutrition and maldigestion along with clinical diabetes and endocrine dysfunction complicate the clinical course of chronic pancreatitis. Early identification of prediabetes among CP patients can halt the progression of dysfunction of B cells that can prevent clinical manifestations of T3cDM. Hence screening of patients with CP for their glycemic index by periodic estimations of fasting blood glucose, HbA1C levels and if necessary glucose tolerance test remain important prevention strategy for T3cDM.

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