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TYPE 3C DIABETES MELLITUS (PANCREATOGENOUS DIABETES MELLITUS) - A REVIEW

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Abstract:

Type 3c diabetes mellitus or pancreatogenic diabetes mellitus is usually misdiagnosed as type 2 diabetes and they may co-exist. Type 2 diabetes is approaching an epidemic worldwide, thus a considerable proportion may be due to type 3c diabetes mellitus. In addition to insulin deficiency, glucagon and pancreatic polypeptide are also lost in type 3 diabetes, so these patients are more prone to hypoglycemia on one hand and a higher microvascular complication on the other hands. Furthermore, failure to introduce the proper treatment in a timely appropriate manner may complicate the matter further with deleterious consequences. Type 3c diabetes mellitus needs a special consideration regarding the diagnosis and management, thus we conducted this review. A systematic manual search was conducted in PubMed and Google Scholar database, articles in English language published from 2009 up to October 2018 were retrieved using type 3c diabetes, pancreatogenous diabetes, pancreatectomy and type 3c diabetes, pancreatitis and type 3c diabetes, and pancreatic cancer and type 3c diabetes, . A total of 209 manuscripts were found, 28 articles were approached after removing irrelevant articles and duplication. In this review we discuss the prevalence, pathophysiology, causes, the diagnosis, and management of this common morbid disease.

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INTRODUCTION:

Pancreatogenic, or type 3c, diabetes is due to acquired or inherited pancreatic disease or resection. Pancreatogenic diabetes has a unique pattern of metabolic hormonal characteristics and a high incidence of pancreatic carcinoma in the majority (1).

Despite the high rate of exocrine pancreatic insufficiency reported in the general population and especially in patients with type 2 diabetes, pancreatogenic diabetes or type 3c diabetes is seldom thought of in clinical practice with deleterious consequences due to the delay of introducing the proper management (2).

Type 3c diabetes mellitus is not uncommon and is more common than type 1 diabetes, it is usually misdiagnosed as type 2 diabetes, due to glucagon loss patients with type 3c diabetes are more prone to hypoglycemia and diabetes control is further compromised by malabsorption, poor diet, and in some alcohol consumption, hence more diabetes complications. The therapeutic goals and clinical characteristic differ from type 1 and type 2 diabetes (3).

SUBJECTS AND METHODS:

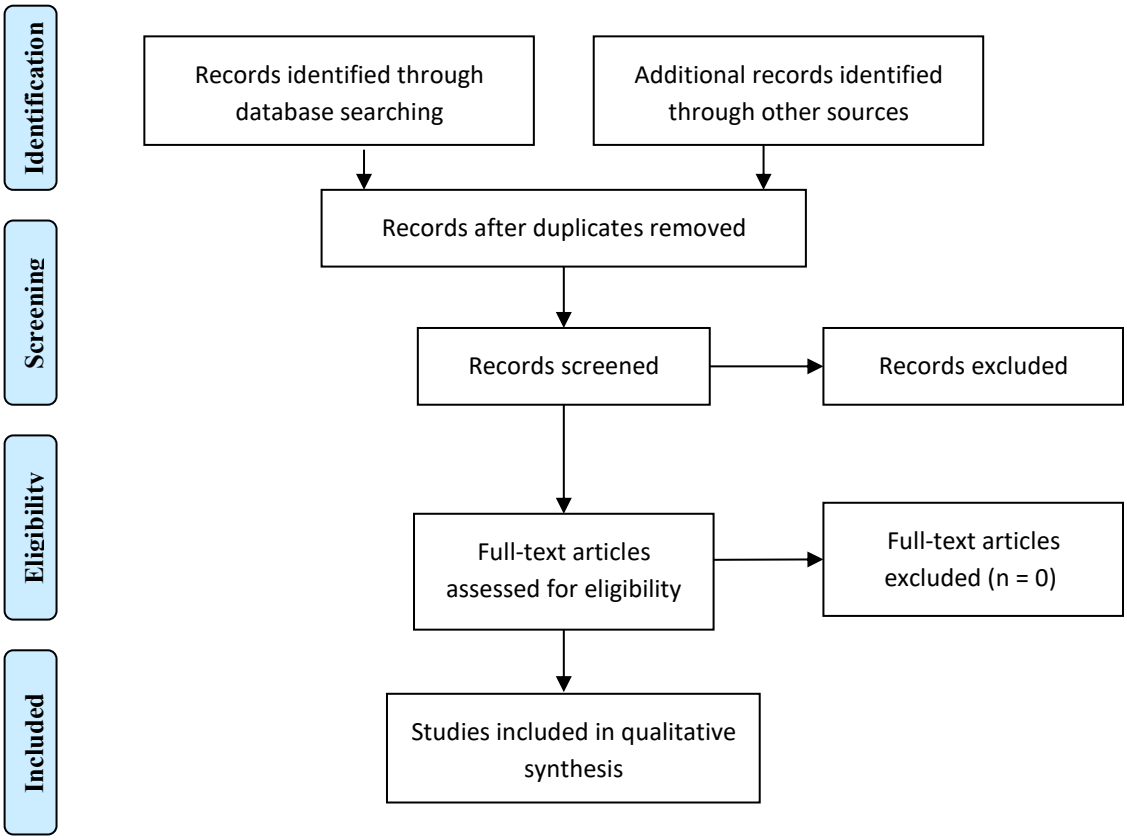
Information sources and search methods:

The pubMed and Google database were searched for relevant articles in English language during the period from January 2009 to October 2018.

Study selection and data extraction:

A manual search was conducted for relevant articles, the following terms were applied: type 3c diabetes, pancreatogenous diabetes, pancreatectomy and type 3c diabetes, pancreatitis and type 3c diabetes, and pancreatic cancer and type 3c diabetes, . A total of 209 manuscripts were found, 28 articles were approached after removing irrelevant articles and duplication. A narrative review was then conducted under the headings, prevalence, pathophysiology, diagnosis, causes, investigations, and management. Figure 1. (PRISMA) depicted the different phases of the systematic review.

Figure 1 - Flow diagram through the different phases of the systematic review (PRISMA flowchart).



PREVALENCE:

Type 3 c diabetes mellitus accounts for 5-10% of Western diabetic populations and is associated with mild to severe disease, 75% of T3c DM is due to chronic pancreatitis which is associated with a high rate of malignancy. A study conducted among patients with pancreatic disease (2) found type 3 diabetes in 9.2% of patients, 78.5% were due to chronic pancreatitis, 6.9% with hereditary hemochromatosis, 8.1% with pancreatic cancer and 3.5% with cystic fibrosis. Only 51.2% were classified correctly, while the remaining were misclassified as type 2 diabetes.

Chronic pancreatitis:

The awareness regarding the development of diabetes in a patient with chronic pancreatitis is good, however chronic pancreatitis in a patient with newly discovered diabetes is usually missed resulting in the delay of the proper replacement therapy in the form of nutrient supplementation. It is important to note that, subclinical chronic pancreatitis is not uncommon. Clinically overt steatorrhea is usually not observed until over 90% of exocrine pancreatic function.The cause is usually the destruction of islet cell due to inflammation, furthermore, the nutrients loss leads to the reduction of incretin response (3,4).

Pancreatoduodenectomy:

After pancreatoduodenectomy 16% develop diabetes, no difference in diabetes risk when pancreatoduodenectomy was performed for the nonmalignant disease after excluding patients with chronic pancreatitis (5).

Pancreatic cancer:

Type 3c diabetes mellitus is a consequence of pancreatic cancer in 30%, and those patents are at high risk of cancer especially those with chronic pancreatitis (6). Patients with long-standing pancreatitis, prior partial pancreatectomy, and early calcific changes on imaging are at high risk and should be followed by annual HbA1c and fasting plasma sugar (7).

Acute pancreatitis:

A study published by Ewald et al. (8) found that among patients with acute pancreatitis followed after a mean duration of 2.7 years pancreatitis developed in 14% of patients and more in patients with severe acute pancreatitis (AP). There were no statistically significant differences according to gender, etiology, and number of AP attacks. Exocrine pancreatic insufficiency (EPI) in diabetic patients is frequent. Studies based on fecal elastase-1 measurement give prevalence rates of 10–30 % of severe and 22–56 % of moderate EPI in type 1 and rates of 5–46 % in type 2 diabetic patients (9).

By using the prevalence of diabetes among patients with the above disorders yield a prevalence of 0.5-1% of all the patients with diabetes. A cohort study reported a prevalence of 9.2% of type 3c diabetes among patients with diabetes, but a question remained to be solved: Is this a primary effect of exocrine pancreatic disease or is it due to a secondary effect of diabetes also termed diabetic exocrine pancreatopathy. Currently the prevalence ranged from1% to 9% of patients with diabetes (10). In region where fibrocalculous pancreatitis is common like southeast Asia rates as high as 20% were observed. a significant elevation in interleukin-6 and endothelin-1 concentration and amylase and lipase were observed among patients with pancreatitis and diabetes who smoke cigarettes indicating a pro-inflammatory response and exocrine-endocrine disturbance (11).

PATHOPHYSIOLOGY IN PANCREATIC CANCER AND PANCREATECTOMY:

Inflammatory markers were found to be high in Pancreatic ductal adenocarcinoma, (C-reactive protein [CRP]) and an inflammatory mediator (TNF superfamily member 13 [TNFSF13]) were found in the serum of patients with PDAC-DM. After surgical resection of PDAC lesions, CRP and TNFSF13 levels significantly decreased (10).Patients with pancreatic cancer showed hyperinsulinemia regardless of the tumor size, thus tissue destruction is unlikely the cause. The mechanism is probably due to a substance secreted by the tumor. Adrenomedullin has been shown to module β cell dysfunction (10).

High levels of interleukin-6 and endothelin-1 and the low levels of insulin and glucagonsuggest a pro-inflammatory effect that disturbs the exocrine-endocrine interactions of the pancreas (12). There are nineteen genes identified in the signature of type 2 diabetes not found in type 3c diabetes. Lack of this signature in islets from PPP with IGT or type 3c diabetes indicates differences possibly due to peculiarities of these hyperglycemic conditions and a role for duration and severity of hyperglycemia (13). Furthermore a cationic trypsinogen (PRSS1) gene mutation for hereditary pancreatitis (14).

DIAGNOSIS:

History and clinical examination together with:

1. The deficiency in postprandial pancreatic polypeptide release, the Human pancreatic

polypeptide is similar in chronic pancreatitis (CP) and pancreatic ductal adenocarcinoma regardless of hyperglycemia (15, 6). Subjects with PaCDM have a blunted PP response to a mixed meal compared to T2DM. However, the blunted PP response is only observed in those PaC subjects with a tumor located in the head of the pancreas (16).

2. Fecal elastase-1 measurement.

Fecal elastase 1 is reduced in marked chronic pancreatitis rather than mild (17). Furthermore, FE-1 was found to be low (<200microgram/g) in 14.2% and 20.9% in patients with type 1 and type 2 diabetes respectively compared to healthy controls (2.5%). FE-1 was found to be reduced in other gastrointestinal disorders including non-ulcer dyspepsia (18,19). A recent review showed that about a quarter of patients with acute pancreatitis develop exocrine pancreatic insufficiency (20).

Criteria for the diagnosis 16:

Major criteria (all should be present):

- The presence of pancreatic exocrine insufficiency
- The presence of pathological imaging (CT, endoscopic ultrasound, and MRI)
- And absence of type 1 diabetes associated autoimmunity

Minor criteria:

- Impaired β-cell function (as measured by homoeostatic model assessment for β-cell function, or C-peptide or glucose concentrations)
- Absence of insulin resistance (as defined by homoeostatic model assessment for insulin resistance), impaired incretin secretion (glucagon-like peptide-1 [GLP-1] or pancreatic polypeptide, or both), and low serum concentrations of lipid soluble vitamins (A, D, E, and K). Lack of standardization of the above tests methods, and the features overlap in long standing type1 and type2 diabetes mellitus are major limitations of the minor criteria.

DIFFERENTIAL:

Celiac disease (with a prevalence of about 3-5 % of type 1 diabetic patients),

Autonomic neuropathy

Irritable colon

And gastrointestinal tumors have to be taken into account. Patients with symptoms and a fecal elastase-1 < 100 µg/g should be treated with pancreas enzymes inadequate daily doses administered at main meals

Chronic pancreatitis:

The commonest cause of type 3c diabetes. The major criteria are: fulfillment of the diagnostic criteria for diabetes mellitus, and the diagnostic criteria for chronic pancreatitis, and exclusion of other potential causes of diabetes. The causes of hyperglycemia are insulin deficiency due to destruction by fibrous tissue, impaired insulin secretion, inflammation, and insulin resistance both in the liver and periphery (21).

DIABETES MELLITUS AND CANCER:

Both type 1 and type 2 diabetes increase the risk of cancer by two folds especially pancreatic cancer, on the other hand, 's cancer can lead to type 3 c diabetes (22). Cancer in diabetes can be reduced by an aggressive approach to reversing obesity and hyperinsulinemia, achieving good glycemic control in diabetic patients, and identifying earlypoint those patients with pancreatogenic diabetes. Diabetes and chronic pancreatitis are risk factors of Pancreatic Ductal Adenocarcinoma and a genomic link between the three diseases are suggested (23).

TREATMENT:

It is often asserted that >90 % of the pancreas must be damaged before exocrine insufficiency occurs; Loss of the pancreatic islet cells occurs later in the disease process as the endocrine cells are diffusely distributed throughout the pancreatic parenchyma. Patients may develop type 3c (pancreatogenic) diabetes, which is complicated by concurrent decreased glucagon secretion, and hence an increased risk of hypoglycemia. Diabetes control is further complicated by poor diet, malabsorption and (for some) alcoholism, and therefore those with type 3c diabetes have clinical characteristics and therapeutic goals that are different from that of type 1 and type 2 diabetes patients (24).Diabetes of the exocrine pancreas is frequently labeled type 2 diabetes but has worse glycemic control and a markedly greater requirement for insulin (3).Pancreatic enzyme replacement therapy is highly variable with low doses associated with unintentional weight loss and gastrointestinal symptoms. (25).

Metformin:

Metformin is the first line as it may reduce the risk of pancreatic ductal adenocarcinoma unlike insulin.

DPP4 Inhibitors and GLP-1 analogues: May increase the risk of adenocarcinoma. DPP-4 inhibitors and GLP-1 analogues may also increase the risk of acute pancreatitis.

Following pancreatectomy: Continuous subcutaneous insulin infusion showed lower hypoglycemia compared to multiple daily injections (26).

Nutrients supplementation:

pancreatic enzyme replacement therapy may increase the insulin and GLP-1 response at least among patients with chronic pancreatitis. Adequate oral pancreatic enzyme replacement and fat soluble vitamins are important to prevent malnutrition, enhance incretin secretion, and improve hyperglycemia.

Pancreatic polypeptide:

Subcutaneous infusion of Pancreatic polypeptide has been shown to enhances insulin sensitivity and reduces insulin requirements in patients with long-standing type 1 and T3c diabetes mellitus on insulin pump therapy (27). Pancreatic polypeptide in sterically stabilized micelles is a promising novel anti-diabetic nanomedicine that is shown to be effective in type 3 diabetes (28).

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