



ADVANCES IN THE UNDERSTANDING OF PATHOPHYSIOLOGY OF TYPE 2 DIABETES MELLITUS

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Conflicts of Interest: Nil

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Abstract:

Type 2 Diabetes Mellitus (T2DM) is a major healthcare concern due its complications like heart disease, cerebro-vascular accidents, etc. It produces a major strain on the healthcare setting as no complete cure is currently available for the disease. This lack of a permanent cure is mainly attributed to the complex pathophysiology of the disease. Multiple factors contribute in the pathogenesis of the disease. Many of such factors have been identified in the recent years. These factors include β cell dysfunction, inflammatory cytokines, NLRP3 inflammasomes, etc.

Keywords: Diabetes, pathophysiology, factors

Introduction

Among the various metabolic diseases, diabetes is an important concern for healthcare professionals all over the world. This is mostly attributed to the higher risk of severe complications like heart disease, cerebro-vascular accidents and renal failure. Type 2 Diabetes Mellitus (T2DM) is also the most common metabolic disease. It is mainly due to defective insulin secretion. Lifestyle factors like age, pregnancy, obesity, etc. have a strong influence on the pathogenesis of such defective insulin secretion [1,2]. In 2017, the number of diabetic patients between 18 and 99 years of age was approximately 451 million. And by 2045, it is expected to reach 693 million. The mortality in case of diabetes in the age group of 20 to 99 is about 20 million [3].

Previously, using insulin radioimmunoassay, it was found out that insulin was secreted in response to nutrient ingestion in case of early maturity onset diabetes patients [4]. Also, the islet β cells of these patients were found to be defective. They failed to mount adequate response towards intravenous secretagogues [5]. Insulin insensitivity was also found among these patients [6]. This led to increased gluconeogenesis in liver along with decrease in the uptake of glucose in muscle and adipose tissue [7].

Type 1 Diabetes Mellitus is mostly treated by insulin therapy throughout the life of the patient [8]. But in case of T2DM, no such long lasting treatment is available due to the complex pathophysiology of the disease, most of which is still unknown to the healthcare professionals. In this review, we have tried to include all the new advances in understanding this complex pathophysiology.

Methods

Here we have systematically reviewed the different articles published from 1936 to 2020 for this purpose from different databases of PubMed, Cochrane Library, etc. Keywords related to the study aim and included in the

search string were: drowning, diagnostic tests, biomarkers, forensic diagnosis. The aim of this article is to highlight newer methods that can be used to diagnose the cause of death in case of drowning.

Role of β cells in glucose homeostasis

The glucose homeostasis is maintained by a feedback loop. It regulates the glucose concentration and maintains it within a narrow range [9]. This interactive signaling between β cells and insulin-sensitive tissues is the mainstay of this feedback loop. Glucose, amino acids and fatty acids are taken up by the insulin sensitive tissues through the mediation of insulin released as a result of β cell stimulation. These islet cells are signaled by these insulin sensitive tissues about their need for insulin. The secretion of insulin from β cells is increased in case of insulin resistance in order to maintain normal glucose tolerance [10].

Impaired glucose tolerance indicates the presence of insulin resistance. In case of impaired glucose tolerance, the rise of glucose concentration even within the normal limit is attributed to decreased β cell function [11]. The evolution of natural history of T2DM from impaired glucose tolerance is due to progression of the deterioration of β cell function [12,13]. The differences in the rates of T2DM in different ethnic groups is attributed to the heritable nature of β cell function [14,15].

Genetic Factors

PPARG was the first gene identified to be associated with T2DM [14]. More than 50 gene loci have been found to be linked to T2DM from genome-wide association studies [16]. Among these gene loci, most of the loci are associated with β cell function. The rest of the loci are linked with insulin resistance and obesity [17]. The risk of development of T2DM in an offspring is increased by certain genetic expressions which are influenced by the in-utero environment [18].

Environmental Factors

The development of obesity, β cell dysfunction, insulin resistance and glucose intolerance have been attributed to increased intake of dietary fats, specially saturated fats [19]. The response of β cells to carbohydrate gets reduced gradually with the progression of age. This results in the decrease of glucose tolerance with ageing [20].

Reduction of β cells

The number of β cells gets reduced in T2DM [21-24]. Multiple factors are responsible for this reduction of β cells. These factors include glucolipotoxicity [25] and deposition of amyloid which cause β cell apoptosis through oxidative and endoplasmic-reticulum stress [24]. Since the human pancreas is not able to produce β cells after 30 years of age, this loss is not replaced by new β cells [26].

α cell dysfunction

In the pancreatic islets, blood flows from β cells to the α cells [27]. It has been found that high concentrations of insulin in the blood flowing to α cells can suppress the release of glucagon [28].

The failure to suppress glucagon release after ingestion of food leads to hyperglycemia. This failure is indicated by increased concentration of fasting glucagon and is attributed to α cell dysfunction [29].

Role of intestine

In the gastro-intestinal tract, Glucagon like peptide 1 (GLP-1) and glucose dependent insulintropic polypeptide (GIP) act on pancreatic islets. Among them, GLP-1 acts on β cells to increase insulin secretion and on α cells to decrease glucagon secretion [30]. There is no difference in GLP-1 concentration between a healthy person and a person having T2DM [31]. Thus, the β cell response to GLP-1 is decreased in case of T2DM. This decreased response has been observed through intravenous administration of GLP-1 under controlled conditions [32].

Another important regulator of glucose metabolism in the gastro-intestinal tract is bile acids. They initiate the release of fibroblast growth factor (FGF) 19 by activating farnesoid X receptor [33]. FGF 19 has insulin-like effects. GLP-1 secretion is also mediated by bile acids through the activation of G-protein-coupled bile-acid receptor 1 located on intestinal L cells [34].

The intestinal microbiome is another important factor in the evolution of T2DM [35]. But which bacterial species are associated with T2DM is not clear [36]. Proof of concept study has shown that infusion of intestinal microbiota from lean individuals can improve insulin sensitivity in patients with T2DM [37].

Role of nervous system

Glucose metabolism is controlled by parasympathetic and sympathetic nervous systems. Direct control is through neuronal input and indirect control is through circulation. Ultimately, the glucose metabolism is controlled through regulation of insulin, glucagon secretion and gluconeogenesis by the nervous system [38,39].

The vagus nerve has been identified to have regulatory effect on the pancreatic islets as experimental severing of this nerve has resulted in decreased insulin secretion [40]. In the cranium, the hypothalamus has been identified as an important regulator of pancreatic islets. This has been shown by the fact that experimental ablation of hypothalamus in rats lead to β cell dysregulation and hyperinsulinaemia [41].

Decreased quality of sleep and changes in diurnal patterns are responsible for alteration of metabolic processes. Hence, the clock genes which maintain circadian rhythm are suspected to play a role in the pathogenesis of T2DM [42,43].

Islet inflammation

Several systemic inflammatory markers like C-reactive protein and Interleukin 6 are associated with β cell function and insulin sensitivity [44,45]. Intra-islet immune response is responsible for β cell dysfunction [46].

Interleukin 1 β and interleukin 1 receptor antagonist concentrations have been found to be increased in case of T2DM. They play a role in inflammation of islet and β cell dysfunction [47,48].

Role of Macrophage-inhibiting cytokine-1 (MIC-1)

MIC-1 regulates body weight by acting on the feeding centers in hypothalamus and brainstem [49]. Insulin activity increases with increase in MIC-1 expression [50]. Hence, MIC-1 can be considered as an anti-inflammatory cytokine and may help in the regression of T2DM.

Role of NLRP3 inflammasome

The NLRP3 inflammasome interacts with the TXNIP and thereby regulates the innate immune system. It is activated by glucose, saturated fatty acids and uric acid. It promotes the production of IL-1 β and cytokines which lead to inflammation of pancreatic islets [51,52].

Role of macrophages

T2DM is characterized by macrophage infiltration of the pancreatic islets. The degree of infiltration is usually proportional to the degree of β cell dysfunction [53-58].

Conclusion

T2DM is one of the most prevalent diseases in today's world. It is a major healthcare concern due to its severe complications like stroke, cardiovascular diseases, etc. Due to its complex pathophysiology, there is no complete cure for this disease. This complex pathophysiology is mainly attributed to the disease being multifactorial. Various studies have shown that the contributory factors to the pathogenesis of T2DM are β cell dysfunction, intestinal and brain signals, NLRP3 inflammasomes, genetic and environmental factors, etc. Further studies need to be conducted to ascertain a more clear picture of the roles of various contributory factors in order to properly understand the pathogenesis of T2DM.

Keywords

T2DM: Type 2 Diabetes Mellitus

GLP-1: Glucagon like peptide 1

GIP: Glucose dependent insulinotropic polypeptide

MIC-1: Macrophage-inhibiting cytokine-1

NLRP3: Nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3

TXNIP: Thioredoxin-interacting protein

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