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INTRODUCTION

Diabetes mellitus is a chronic disease that results from; relative or absolute insulin deficiency, insulin resistance, or both and could be classified according to the etiology of the disease (1). Genetic and environmental factors could contribute to diabetes mellitus and its complications. The diabetes mellitus prevalence in the world in 2019 is estimated to be 9.3% (463 million people), increasing to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 (2). Genetic and environmental factors can be the cause of this chronic metabolic disorder (1). Diabetes mellitus causes acute and chronic complications, which affect many organ systems. If left untreated, as a result of long-term hyperglycemia, these complications result in morbidity and mortality. Long-term hyperglycemia is known to be related to oxidative stress and chronic inflammation (3-5). Chronic complications of diabetes mellitus are classified as vascular and non-vascular complications. Types of vascular complications are also classified as microvascular and macrovascular (1,6). Microvascular complications of this metabolic disorder are retinopathy, neuropathy, nephropathy. Macrovascular complications are coronary heart disease, peripheral arterial disease, cerebrovascular disease. In this review, we aim to discuss chronic complications of diabetes mellitus and the pathogenesis

Pathogenesis of chronic complications of diabetes mellitus

Abstract

Diabetes mellitus is a chronic disease that results from; relative or absolute insulin deficiency, insulin resistance, or both. The prevalence of the disease is increasing all over the world and it causes severe socioeconomic consequences, especially with its chronic complications. When possible genetic and environmental factors are evaluated; lifestyle changes, sedentary life and obesity are considered as serious reasons for this increase in prevalence. Chronic complications of the diabetes arise from various biochemical mechanisms. And these chronic complications are responsible for organ failure in a large number of diabetic people every year. In the diabetes process, it is of great importance to understand and manage chronic complications well in order to slow down or prevent complications. This article is a mini-review designed to explain the biochemical mechanisms of chronic complications of diabetes.

Keywords: Diabetes Mellitus; Chronic complications; Genetics; Pathogenesis; Molecular mechanisms

of these complications.

Pathogenesis of Diabetes Mellitus Complications

Genetic factors, molecular mechanisms, or both may lead to chronic complications of diabetes mellitus (1). Complications are related to the thought which this disease is a process of chronic inflammation and oxidative stress. Functions of endothelial capillary cells are impaired by-products of this inflammation (7). Oxidative stress disproportionates oxidant and antioxidant systems, elevated free radicals, and reactive oxygen species. Chronic hyperglycemia is the leading cause as it triggers the molecular mechanisms that cause complications; however, lipid catabolism defects and overproduction of reactive oxygen species are also causes of chronic complications (3). These molecular mechanisms fall into four main groups:

- Increased polyol pathway
- Increased hexosamine pathway
- The increased intracellular advanced glycation end product (AGE)
- Activation of protein kinase C

In addition to these molecular mechanisms, increased immune cell

activations are thought to be one of the reasons for complications (5).

Increased Polyol Pathway

The polyol pathway is the cascade in which glucose is converted to sorbitol by aldose reductase, and sorbitol is converted to fructose by sorbitol dehydrogenase (3). This pathway could also be named the sorbitol-aldose pathway. This pathway is activated when glucose quantity is increased. Hyperglycemia in the blood raises aldose reductase activity; as a result of this, the conversion of glucose to sorbitol increases. Increased quantity of sorbitol in the intracellular region causes osmotic detriment and oxidative damage (3). Henceforth, sorbitol is converted to fructose by sorbitol dehydrogenase. Accelerated activation of these enzymes decreases NADPH essential for antioxidant function in the body; therefore, oxidative damage occurs (1). In addition to decreased NADPH, increased sorbitol leads to hydration and membrane damage by generating osmotic stress. Also, fructose is a reason for glycation stress (Glycative stress).

Increased Hexosamine Pathway

Normal glycolysis pathway occurs in the body as long as there are normal glucose levels in the blood (3). However, if there is an increased glucose level in the blood, this normal pathway turns into the hexosamine pathway by supplying more fructose - 6 - phosphate. This alteration increases oxidative stress because of the overproduction of uridine diphosphate-N-acetyl glucosamine, known as UDP-GlcNac. N-acetylglucosamine, produced by splitting to serine and threonine, induces the factors that promote complications such as PAI-1 or TGF- β (1). Increased levels of PAI-1 and TGF- β induce fibrosis, vascular atherosclerosis, and mesangial cell injury. In addition to these mechanisms, N-acetyl glucosamine leads to elevated hydrogen peroxide levels, impairs normal glucose metabolism, and could affect gene expressions of glucose metabolism pathway genes (3).

Increased Intracellular Advanced Glycation-end Product (AGE)

Glucose undergoes autooxidation in the cell when it maintains chronically elevated levels (3). By this oxidation, generating of dicarbonyls is increased. Dicarbonyl species, called advanced glycation end products (AGE), are methylglyoxal, glyoxal, 3-deoxyglucosone. AGEs transmute normal metabolic functions of cells and gene expression of DNA. AGEs also lead to the alteration of extracellular matrix proteins, and by this alteration, AGEs damage cellular signaling mechanisms. These altered proteins induce the expression of IL-1, IGF-1, TNF- α , TGF- β , VCAM-1, VEGF by binding to receptors of endothelial cells and macrophages (1).

Activation of Protein Kinase C

Diacylglycerol induced by hyperglycemia activates the protein kinase c pathway. Activation of the protein kinase c pathway results in activation of protein kinase c isoforms such as β and δ . These isoforms increase diabetic complications by

stimulating the production of VEGF, TGF- β , PAI-1, NF- κ B, MGO(methylglyoxal), NADPH oxidases (1).

All of these mechanisms stimulate increased production of superoxide, and they are causes of diabetic complications. In addition and related to these mechanisms, hyperglycemia induces overproduction of reactive oxygen species known as ROS. Some specimens of ROSs are hydroxyl(HO $\cdot$), hydrogen peroxide (H $_2$ O $_2$), superoxide anion(O $_2^{\cdot-}$) and of these specimens, for oxidative radicals, superoxide anion is the primary molecule because of is convertible to other oxidative products. Reactive oxygen products are products of aerobic metabolism pathways of mitochondria, peroxisomes, endoplasmic reticulum. Oxidative injury occurs when these molecules are produced at high levels or removed in small quantities. Reactive oxygen species lead to inflammation in kidneys, pancreas, liver, endothelial cells, nerves, and eyes (4).

Genetic and Epigenetic Factors for Diabetes Mellitus and Complications of Diabetes Mellitus

Insulin genes settle on the short arm of chromosome 11 (1). Underlying genetic and epigenetic factors of diabetes mellitus are topics of interest and research (7). Especially Type 2 Diabetes Mellitus has an intense genetic background, but this genetic background generally does not correspond with the Mendelian pattern; also, this disease fits the heterogeneous pattern (1). Diabetes Mellitus may be monogenic or polygenic. For example, TCF7L2, a transcription factor in Wnt signaling, and variants of the gene encoding TCFL2, is related to an increased risk for diabetes mellitus. Some autosomal dominant genetic defects of pancreatic β cells are related with defects or various mutations of these genes; HNF4A, GCK, HNF1A, PDX1, HNF1B, NEUROD1, KLF11, CEL, PAX4, BLK, APPL1, GATA4, GATA6, INS, KCNJ11, ABCC8. Some autosomal recessive genetic defects of pancreatic β cells are related with defects or various mutations of these genes; GCK, PDX1, PTF1A, NEUROG3, RFX6, GLIS3, NKX2-2, MNX1, EIF2AK3, IER3IP1, WFS1, SLC19A2 (1). In addition to these genetic factors, micro RNA abnormalities may be responsible for the diabetes mellitus process. MicroRNA, known as miRNA, are the molecules that affect their target genes in a post-transcriptional stage (7). In diabetes mellitus duration, they lead to endothelial dysfunction, impaired lipid metabolism, and inflammation process. In the future, diagnostic studies and treatment modalities for diabetes, and complications of diabetes, would be more beneficial with the increase of research and knowledge about the genetic background of diabetes mellitus.

Chronic Complications of Diabetes Mellitus Complications of diabetes can be divided into acute and chronic. In this review, our focus was chronic microvascular complications of diabetes. Diabetes leads to complications in vascular tissue, nerves, lens, skin. These complications are divided into two main groups: microvascular and macrovascular (1). These complications are related to increased morbidity and mortality, decreased quality of life, extremity loss, vision loss, organ failure, or loss. Because of

diabetes, personal and social life worsening results, diabetes and its complications are significant.

Microvascular Complications

Microvascular complications are retinopathy, nephropathy, neuropathy and occur by capillary basement membrane injury, small vessel disease, defect of vascular permeability, high water retention, injury of angiogenic cells, generalized edema, impairment of tissue neogenesis. Microvascular complications of diabetes are related to decreasing or loss of visual functions, kidney failure, sexual dysfunction, and peripheral neuropathy.

Diabetic Retinopathy

Diabetic patients, especially ones who have been diabetic for more than five years, should be referred to an ophthalmologist in their follow-up process (6). There can be macular edema in every diabetic patient, but diabetic retinopathy divides into two main categories: non-proliferative and proliferative retinopathy (6).

By activation of the protein kinase c pathway, diabetic vascular complications increase because of elevated cellular permeability (3). In addition to this mechanism, hyperglycemia and oxidative stress accelerate diabetic retinopathy.

Diabetic Nephropathy

Because of diabetes mellitus, diabetic nephropathy is responsible for 4000 cases of end-stage renal disease in the United States, and renal failure occurs in one-third of all patients (1). The initial clinical finding of diabetic nephropathy is proteinuria, and albumin excretion could be the first sign for diabetic nephropathy (6). Nodular intercapillary glomerulosclerosis, known as Kimmelstiel-Wilson lesions, is less common than diffuse glomerulosclerosis (1).

In diabetic patients, glomerular endothelial cell barrier and endothelial basement membrane injury occur because of oxidative stress; therefore, protein filtration increases. Angiotensinogen gene expression is affected by oxidative stress (3). AGEs lead to stimulation of cytokines; by this mechanism, diabetic nephropathy could worsen.

Diabetic Neuropathy

Peripheral and autonomic neuropathies occur in chronic hyperglycemia and manifest as gastroparesis, incontinence, sexual dysfunction, and distal symmetric polyneuropathy. In autonomic neuropathy, digestive systems functions are impaired; therefore, it manifests as nausea, vomiting, abdominal pain, heartburn, slowed stomach emptying, constipation, diarrhea, and gastrointestinal tract infections. Because neuropathy leads to loss of sensation, diabetic foot disease occurs in peripheral diabetic neuropathy. Chronic hyperglycemia in the blood leads to an activated polyol pathway, and therefore as addressed before, this pathway diminishes NADPH. In addition to these mechanisms, the sorbitol pathway is also responsible for nerve cell damage (3). Increased free radicals worsen erectile dysfunction and impair ejaculation.

Macrovascular Complications

Macrovascular complications are coronary arterial diseases and peripheral arterial diseases; complications manifest as myocardial infarction, stroke, peripheral vessel disease; and they occur by extensive vessel injury, accelerated atherosclerosis, and impaired lipid metabolism. This complication occurs by over-production of ROS, vasoconstriction, and impairment of lipid metabolism. In diabetic patients, microangiopathy occurs and leads to cardiomyopathies.

Other Complications of Diabetes Mellitus

Skin pathologies occur in diabetes because of poor glycemic control and manifest as candidal infections, vulvovaginitis, necrobiosis lipoidica diabetorum. These are complications caused by increased glucose delivery to the skin and dehydration of the skin.

Bone and joint complications occur by over-production of glycation-end products and manifest as Dupuytren contractures, Carpal tunnel syndrome, diabetic cheiroarthropathy (Diabetic stiff hand syndrome or limited joint mobility syndrome), diffuse idiopathic skeletal hyperostosis, bursitis, decreased bone mineral density (1).

Conflict of interests

The authors declare that they have no competing interests.

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