The Pathophysiology of Diabetes

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Diabetes mellitus (DM) comprises a range of metabolic disorders characterized by high blood glucose levels caused by defects in insulin release, insulin action, or both. DM is a widespread condition that affects a substantial portion of the global population, causing high morbidity and mortality rates. The main symptoms of diabetes include increased blood glucose, excessive thirst, frequent urination, impaired vision, hyperphagia, weight loss, nausea, and vomiting.

diabetes insulin glucose complications T1DM T2DM

1. Introduction

Diabetes mellitus (DM) is a severe medical condition that affects how the body processes glucose in the blood. It can develop following either a deficiency in the production of the anabolic hormone insulin or a lack of insulin sensitivity from cells or both. The resulting excess sugar in the blood leads to abnormalities in the metabolism of carbohydrates, lipids, and proteins. Insufficient production of insulin can also lead to these disruptions [1][2]. Diabetes is a widespread condition that affects a substantial portion of the global population, causing high morbidity and mortality rates and resulting in a major public health crisis. In 2021, it was estimated that over half a billion people have diabetes. This number is predicted to continue to rise, with 783.2 million people expected to live with diabetes by 2045 [3]. Diabetes is considered one of the five most severe diseases worldwide.

Type 1 and Type 2 are the two most widespread forms of diabetes. Type 2 diabetes mellitus (T2DM) accounts for the majority of diabetes cases (approximately 90–95% of cases). Among type 1 diabetes patients, about 85% are reported with islet cell antibodies, which act against cells from the islets of Langerhans, affecting glutamic acid decarboxylase (GAD) function [2]. Type 1 diabetes (T1DM) is generally associated with insulin insufficiency due to the autoimmune destruction of pancreatic β-cells by CD4+ and CD8+ T cells and macrophages. The abnormal functioning of pancreatic α-cells also contributes to the worsening of insulin insufficiency. The α-cells produce an excessive amount of glucagon, which further leads to metabolic disorders. The decreased insulin and glucose metabolism in peripheral tissues contributes to raising the level of free fatty acids in the blood by triggering lipolysis. As a result, the target tissues fail to exhibit normal insulin responsiveness due to a deficiency in the glucokinase enzyme in the liver and glucose transporter (GLUT)-4 protein in adipose tissues [2]. On the other hand, the progression of T2DM is usually genetic and associated with obesity triggering a low capacity of β-cells to secrete insulin and insulin resistance [4]. In T2DM, chronic hyperglycemia is frequently observed in blood vessels of the cardiac, renal, and retinal circulation. The excess fat deposition in the blood vessels, heart, or peripheral

tissues exacerbates insulin resistance and contributes to cardiovascular diseases [2]. Gestational diabetes is another type of diabetes that refers to glucose intolerance during pregnancy and heightened fetal–maternal complications [5]. Diabetes is interconnected to both micro and macrovascular complications, including retinopathy, nephropathy, neuropathy, ischemic heart disease, peripheral vascular disease, and cerebrovascular disease. This results in organ and tissue damage in one-third to one-half of all diabetic patients. The precise etiology of this damage remains elusive, although growing evidence suggests that oxidative stress and the generation of free radicals play a significant role [6].

2. The Characteristics and Complications of Diabetes

Diabetes mellitus is a dysregulation of glucose homeostasis either caused by the inability to produce insulin (in Type 1 diabetes) or an insufficient response to insulin (in Type 2 diabetes). DM occurs when the delicate balance of insulin and glucagon secretion in the pancreatic islets of Langerhans is disrupted due to alterations in the functioning of the insulin-producing β cells and glucagon-producing α cells [7]. Diabetes usually develops when fasting plasma glucose levels increase due to insulin resistance in the peripheral tissues (also known as the prediabetes stage). It further progresses to hyperinsulinemia, which is characterized by increased insulin production. The long-term overproduction of insulin causes cell failure, in turn contributing to hyperglycemia [8].

The increase in blood glucose levels beyond the normal physiological range in individuals with diabetes can lead to various complications, including renal, neural, ocular, and cardiovascular disorders, emphasizing the need for an early diagnosis of diabetes [8]. Polyuria serves as a crucial diagnostic hallmark for the early detection of diabetes and as an underlying factor in the pathogenesis of DM [9]. Hyperglycemia has also been shown to activate certain metabolic pathways, which contributes to the pathogenesis of diabetic complications [10]. Among these metabolic pathways, protein kinase C (PKC) activation plays a significant role in hyperglycemia-induced atherosclerosis. PKC activation is implicated in a variety of cellular responses, including growth factor expression, signaling pathway activation, and oxidative stress amplification. Hyperglycemia generally stimulates metabolic processes and increases ROS (reactive oxygen species) generation by activating the polyol and hexosamine pathways resulting in diabetes-induced atherosclerosis. The upregulation of the receptor for advanced glycation end product (RAGE) genes, which regulates cholesterol efflux, monocyte recruitment, macrophage infiltration, and lipid content in diabetic patients, triggers diabetes-induced inflammation [8]. Studies have shown that in diabetic mice, there is an increase in multiple PKC isoforms in the vasculatures of the renal glomeruli and retina. It has been observed that the activation of β- and δ-isoforms appears to be preferential. The activation of PKC in various tissues, including the retina, heart, and renal glomeruli, accompanied by the rise in blood glucose levels, exacerbates diabetic complications [11]. An increase in the total diacylglycerol (DAG) content has also been observed in various diabetic vascular complications, including in “insulin sensitive” tissues like the liver and skeletal muscles in diabetic animals and patients [12]. As a result of their production from glucose-derived dicarbonyl precursors, advanced glycation end products (AGEs) frequently accumulate intracellularly. AGEs are key triggers for the activation of intracellular signaling pathways and the alteration in protein activity [13]. Glycation disrupts the normal function of proteins by modifying their molecular shapes, affecting enzymatic activity, lowering breakdown capacity, and interfering with

receptor recognition. Upon AGE degradation, highly reactive AGE intermediates (e.g., methylglyoxal, glyoxal) are formed. These reactive species are able to produce additional AGEs at a faster rate than glucose itself, fueling the production of AGEs and contributing to the pathogenesis of DM [14]. The pathogenesis of DM also involves the generation of pro-inflammatory mediators and ROS with elevated levels of cyclo-oxygenase (COX)-2, a crucial regulator in the conversion of arachidonic acid into prostaglandins that mediate inflammation, immunomodulation, apoptosis, and blood flow and elevated levels of antioxidant enzymes (glutathione S-transferase (GST), superoxide dismutase (SOD), and catalase (CAT)) counteracting the exacerbated oxidative stress [15].

T1DM is an autoimmune disease primarily seen in children and adolescents. T1DM is associated with the selective destruction of β cells, with no damage to other islets cells such as α cells (that secrete glucagon), δ cells (that secrete somatostatin), and pancreatic polypeptide cells (that modulate the rate of nutrient absorption). The development of T1DM is largely influenced by the rate of immune-mediated apoptosis of pancreatic β-cells. A strong connection has been established between damage to pancreatic β cells and genetics, as studies have revealed that variations in genes of the Human Leukocyte Antigen (HLA) complex increases T1DM susceptibility. In T1DM, mutations in such genes override self-tolerance mechanisms and result in the production of autoantibodies and T-cell cytotoxic to pancreatic β cells. This immune-mediated β-cell destruction and ultimate failure trigger diabetic ketoacidosis (DKA), typically considered the initial symptom of the disease. The presence of autoantibodies is an identifying trait of T1DM. These include autoantibodies to Glutamic Acid Decarboxylase (GADs) such as GAD65, autoantibodies to Tyrosine Phosphatases IA-2 and IA-2α, autoantibodies to the Islet-Specific Zinc Transporter Isoform 8 (ZnT8), Islet Cell Autoantibodies (ICAs) to β-cell cytoplasmic proteins like ICA512, and Insulin Autoantibodies (IAAs) [10][16].

T2DM is a metabolic disorder characterized by increased glucose levels, ROS generation, and inflammation, all of which are linked to obesity. The poor glycemic control in T2DM provokes ROS generation resulting in the stimulation of the redox pathway. Antioxidant enzymes (e.g., SOD, CAT, and GST), as well as COX, are produced. In T2DM, the β Langerhans cells are hypersensitive to glucose in blood plasma. As a result, they produce higher than normal insulin levels. This hyperinsulinemia serves to counteract hyperglycemia, which impairs β cell functions. Chronic hyperglycemia further induces microvascular complications resulting in higher morbidity and mortality [11]. Moreover, the accumulation of AGEs is a primary mediator in the progression of non-proliferative retinopathy in T2DM. The pathophysiological cascades triggered by AGEs also play a significant role in the development of diabetic complications. The accumulation of AGEs in the myocardium, observed in 50–60% of diabetic patients with microalbuminuria, has been linked to diastolic dysfunction and highlights the complex interplay between AGEs, oxidative stress, and diabetic complications [12]. Fatty liver, characterized by fat deposition in hepatocytes, is another key feature of T2DM. The high amounts of dietary lipids and abundance of free fatty acids from adipose tissues to the liver, as well as lipogenesis, are the main reasons for this metabolic imbalance [7]. Insulin resistance predominates in the liver and the muscles. The liver produces glucose from non-glucose substances (gluconeogenesis) in fasting periods to maintain a constant availability of carbohydrates. Increased gluconeogenesis is seen in hyperinsulinemia, suggesting that hepatic insulin resistance is an indicator of fasting hyperglycemia. The accumulation of fat in pancreatic islets ultimately contributes to β-cell dysfunction, leading to an increase in plasma glucose levels and a reduction in insulin response to ingested glucose [10].

Other types of diabetes include Maturity-Onset Diabetes of the Young (MODY) and gestational diabetes. In MODY, mutations occur in certain genes involved in insulin secretion by pancreatic β cells. This leads to a reduction in insulin secretion capacity. Gestational diabetes only occurs during pregnancy as a result of an increase in anti-insulin hormones, leading to insulin resistance and elevated blood sugar levels in the mother [5][10][17]. The presence of faulty insulin receptors can also result in a range of pathophysiological symptoms and complications associated with diabetes, including polydipsia, polyuria, weight loss due to calorie loss in urine, increased appetite (polyphagia), impaired wound healing, susceptibility to gum and other infections, cardiovascular disease, eye damage, kidney damage, nerve damage, and the risk of developing diabetic foot, diabetic ketoacidosis, and non-ketotic hyperosmolarity [17][18].

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