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Review Article

Diabetes Mellitus Induced Oxidative Stress, Inflammation and Apoptosis: A Concise Review

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Abstract

Diabetes mellitus is a non-communicable disease that is characterized by increased levels of glucose in the blood, due to abnormal regulation of carbohydrate, lipid and protein metabolism, caused either due to insufficient insulin secretion or insulin action. Blood glucose elevation or hyperglycemia leads to severe damage to the heart, liver, blood vessels, eyes, kidney, nerves, etc. The primary goal of this review was to demonstrate the fundamentals of oxidative stress, inflammation and apoptosis in diabetes mellitus. Hyperglycemia can promote oxidative stress, inflammation and apoptosis in tissues. Oxidative stress causes a complex dysregulation of cell metabolism and cell-cell homeostasis; in particular, oxidative stress plays a key role in the pathogenesis of insulin resistance and β-cell dysfunction. In general, glucose auto-oxidation and protein glycosylation generate free radicals, leading to a raise in oxidative stress levels in tissues, followed by inflammation and apoptosis in tissues. TNF-α is one of the major cytokines released during hyperglycemia from macrophage and lymphocytes, which increase the inflammation and apoptosis, and may cause micro and macro vascular damage in diabetic patients. Thus, researchers must focus on compounds, which target all the complications of diabetes and also concentrate on improving the overall well-being of the diabetic patients.

Keywords: *Diabetes Mellitus; Hyperglycemia; Oxidative Stress; Inflammation and Apoptosis*

Introduction

Diabetes mellitus, a chronic disease, occurs either when the pancreas does not generate adequate insulin, i.e. a hormone that adjusts the blood glucose level, or the body cannot effectively utilize the insulin it produces [1]. Blood glucose elevation or hyperglycemia is a general effect of uncontrolled diabetes leading to severe damage to the heart, blood vessels, eyes, kidney as well as nerves [2]. Hyperglycemia produces the usual symptoms of polyurea (frequent urination), polydipsia (increased thirst) and polyphagias (increased hunger) [3]. According to the American Diabetes Association (ADA), diabetes mellitus is classified into four types, namely type 1, type 2, gestational diabetes and other type, which include monogenic diabetes, secondary diabetes, etc. All types of diabetes comprise of similar signs and symptoms, but have different causes and population distributions. In all the types of diabetes, the insulin present within the body is unable to ameliorate hyperglycemia [4].

Numerous pathogenic processes are associated with the progression of diabetes. These factors range from the autoimmune destruction of the β-cells of the pancreas to resistance of insulin action. The basis of the irregularities in carbohydrate, fat and protein metabolism in diabetes is the incomplete action of insulin on target tissues. Incomplete insulin actions result from insufficient insulin secretion or reduced tissue stimulus to insulin at one or more stages in the multifaceted action of the hormone. Inadequate insulin secretion or insulin action, at a stage in diabetes may often coexist within a patient and it is frequently unclear which abnormality, either alone or in combination, is the main cause of hyperglycemia [4].

Prevalence of diabetes in the World

According to World Health Organization [5] globally, the diabetic population has raised from 108 million in 1980 to 422 million in 2014. In which the age group of above 18 years old, has raised from 4.7% in 1980 to 8.5% in 2014. Over the past few decades, the prevalence of diabetes has risen faster in the middle-low-income countries than in high-income countries. Diabetes directly caused 1.5 million deaths during 2012 and higher-than-optimal blood glucose involved an additional 2.2 million deaths, thus, by substantially raising the risks of cardiovascular and other associated diseases. Forty-three percent of the total 3.7 million deaths occurred in the people below the age of 70 years in low and middle-income countries than in high-income countries. The majorities of people suffering from type 2 diabetes are the adult population, but now children affected with diabetes is also on the raise [2].

According to the recent estimates, one person in every 11 adults has diabetes. Table 1 exhibits the ten countries with the highest rate of diabetic population in the world recorded during 2015 and there possible raise in the diabetic affected population in 2040 [6].

Rank	Countries	2015 Number of people with diabetes	Rank	Countries	2040 Number of people with diabetes
1	China	109.6 million	1	China	150.7 million
2	India	69.2 million	2	India	123.5 million
3	USA	29.3 million	3	USA	35.1 million
4	Brazil	14.3 million	4	Brazil	23.3 million
5	Russian Federation	12.1 million	5	Mexico	20.6 million
6	Mexico	11.5 million	6	Indonesia	16.2 million
7	Indonesia	10.0 million	7	Egypt	15.1 million
8	Egypt	7.8 million	8	Pakistan	14.4 million
9	Japan	7.2 million	9	Bangladesh	13.6 million
10	Bangla-desh	7.1 million	10	Russian Federation	12.4 million

Table 1: *Top ten Countries for number of people with diabetes (20 - 79 years) 2015 and 2040.*

Diabetes and metabolic abnormalities

Diabetes mellitus is not only connected with carbohydrate metabolism but is also associated with lipid and protein metabolisms, and oxidative stress, which collectively lead to various diabetes associated disorders.

Carbohydrate metabolism

In diabetic condition, glucose metabolism is altered due to the changes in the actions of the enzymes that regulate glycolysis and gluconeogenesis in the liver and muscle, such that the latter process becomes favored [7]. Insulin inhibits glucose production from the liver by triggering glycogen synthesis and suppress glycogenolysis and gluconeogenesis. Liver glucose production is the main risk factor for the development of hyperglycemia, particularly fasting hyperglycemia, in type 2 diabetes [8]. Insulin has the ability to directly influence the substrate availability and changes of free fatty acids (FFA) in liver [9,10]. There are many important enzymatic checkpoints that regulate liver glycolysis and gluconeogenesis (phosphoenolpyruvate carboxykinase, fructose 1,6-bisphosphatase), glycogen synthesis (glucokinase, glycogen synthase kinase-3), glycogenolysis (phosphorylase) or steps that are common to the pathways (glucose 6-phosphatase). Some of these steps are directly influenced by insulin by phosphorylation as well as dephosphorylation [11].

Protein metabolism

Insulin commonly has an anabolic effect on protein metabolism by enhancing protein synthesis [12,13]. Insulin initiates the uptake of neutral amino acids into muscles, an effect which is not connected to glucose uptake or a subsequent incorporation of amino acids into protein. The effect of insulin on general protein synthesis in skeletal and cardiac muscles and liver are exerted at the level of m-RNA translation [14]. In recent years insulin has been shown to influence the synthesis of specific proteins by affecting changes in the corresponding m-RNA [14].

Lipid metabolism

In diabetic patients, due to insufficient insulin secretion, increase lipase activity consequently increase the lipolysis and led to elevated levels of free fatty acid in plasma and liver [15]. The level of glucagon also elevates in diabetic patients and this increases the release of free fatty acids. Free fatty acids are metabolized to acetyl CoA and finally to CO_2 and H_2O via citric acid cycle. In the patient with insulin deficiency, the capacity of this process is rapidly elevated and the acetyl CoA is converted to acetoacetyl CoA and then to acetoacetic and hydroxy-butyric acids [16]. Insulin apparently also affects either formation or clearance of VLDL and LDL, since levels of these particles and levels of cholesterol are often elevated in poorly controlled hyperglycemic patients [15].

Oxidative stress

Oxidative stress is a result of an inadequate balance between free radicals formed and antioxidants present in the system, which are the result of either an elevated radical generation or declined antioxidant levels. Oxidative stress has been implied for a long time as a key process in the development of complications of diabetes mellitus and chronic renal diseases [17,18]. In diabetic patients, increased blood glucose can trigger free radical generation and frail the defense mechanism of the body, becoming incapable of counteracting the elevated levels of reactive oxygen species (ROS) generated and as a result an imbalance between oxidants and pro-oxidants leads to the induction of oxidative stress [19,20].

A small quantity of oxidative stress or ROS is required for the regular metabolic process because ROS plays different regulatory roles in cells [21]. Neutrophils and macrophages generate ROS during the process of the respiratory burst in order to eliminate antigens [22]. ROS also influences many genes signaling which encodes differentiation, transcription factors and development and also stimulates cell-cell adhesion, cell signaling, vasoregulation, fibroblast proliferation, as well as increase expression of antioxidant enzymes [21,23,24]. However, the more or abnormal level of ROS generation is harmful to the body. Due to oxidative stress produced in metabolic abnormalities of diabetes, its causes mitochondrial superoxide overproduction in endothelial cells of both the large and small vessels and in the myocardium [25,26]. The oxidative stress is the major risk for development of insulin resistance and it's sequence of glucose intolerance and installation of diabetes mellitus, then favoring the occurrence of atherosclerotic complications [27].

The antioxidant enzymes and administrations of antioxidant compounds have the ability to recover both triglyceride-associated oxidative stress and diabetic cardiomyopathy [28]. Thus, diabetes mellitus induces oxidative stress leading to injury to multiple organs, which cause several complications. Figure 1 illustrates how diabetes induces oxidative stress induces production of superoxide through several pathways and superoxide further reacts with NO to form peroxynitrate to induce a series of detrimental effects leading to the formation of diabetic complications.

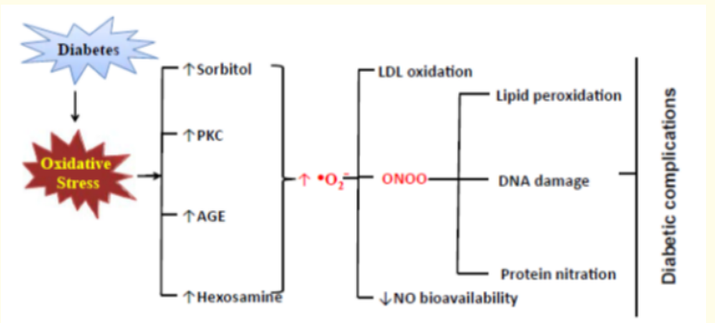

Figure 1: *Diabetic oxidative stress and downstream targets leading to diabetic complications (Didac Mauricio, 2016).*

Insulin signaling pathway

Insulin is the polypeptide hormone that contributes several signaling cascades. The action of insulin is initiated by binding of insulin to the insulin receptor (IR) of target cells, stimulating autophosphorylation of the receptor, evoking the activation of receptor tyrosine kinases and consequently stimulating the tyrosine phosphorylation of insulin receptor substrates (IRSs). The phosphorylation of IRSs

enhances the activation of phosphatidylinositol 3-kinase (PI3K). As a result, AKT/protein kinase B (PKB) and protein kinase C (PKC), i.e. serine/threonine kinases, are activated [29]. The activation of AKT initiates the translocation of GLUT-4 from cytosol to the plasma membrane, resulting in the transport of glucose into the cell [30]. Conversely, the insulin receptor inactivates by dephosphorylation of protein tyrosine phosphatases (PTPs). PTPs involve a family of proteins with negative effects on insulin role [31]. Furthermore, phosphatase and tensin homolog deleted on chromosome 10 (PTEN) have a dual function. Lipid and protein phosphatase are considered as a negative regulator of the insulin signal transduction. PTEN was initially identified as a deleted or mutated tumor suppressor gene in different human cancers.

PTEN antagonises PI3-kinase/AKT pathway by reconverting phosphatidylinositol 3,4,5-triphosphate (PIP3) back to phosphatidylinositol 3,4-bisphosphate (PIP2) [32]. Hence, regulation of insulin role is carried out by the balance of phosphorylation and dephosphorylation. Figure 2 elaborately explains the insulin signal transduction pathway in target cells. The PI3K is supposed to be a crucial constituent of the insulin signal transduction and indispensable for the effects of insulin on GLUT-4 translocation and glucose uptake [33].

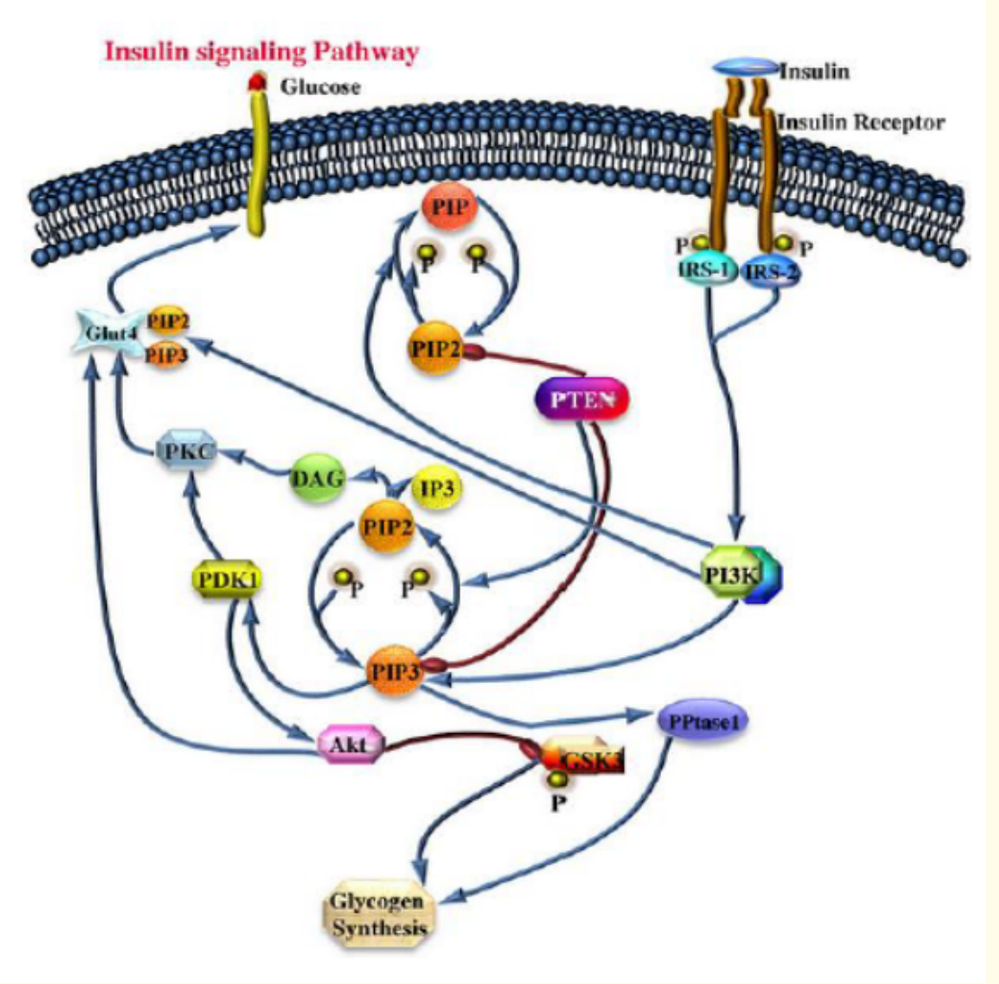

Figure 2: *Insulin signaling pathway and glycogen synthesis (Khorami et al., 2015).*

In diabetic patients, the decline of PI3K activity in skeletal muscle gives evidence for impairment in the insulin signal transduction that may contribute to the impaired translocation of GLUT-4 and insulin resistance. The increased levels of PTEN lead to inhibition of the PI3K signaling pathway due to the impaired glucose uptake. In contrast, reduction of PTEN expression improves insulin stimulated AKT and GSK3 phosphorylation [34]. Thus, elevated level of PTEN may make individuals more susceptible to the development of Type II diabetes.

Diabetes induced inflammation and apoptosis

The chronic hyperglycemia has the ability to directly stimulate an inflammatory state leading to increased cytokine levels, resulting in the destruction of β-cells of the pancreas and disturbance in the functioning of the endocrine portion of the pancreas in both type 1 and type 2 diabetes mellitus [35]. Both type 1 and type 2 diabetes are associated with inflammatory processes [36,37] that are the reason for a notable rise in interleukin (IL) IL-6, IL-18, IL-1 as well as TNF-α in the blood of diabetic patients [38,39]. TNF-α is one of the major cytokines released in inflammatory processes that is capable of activating signaling pathways associated with the cell survival, apoptosis, inflammatory response and cell differentiation. Macrophage and lymphocytes generate TNF-α in response to inflammation and infection [40]. The binding of TNF-α to TNF-R1 is able to enhance the activation of NFκB or initiate the activation of caspases, which contribute to the execution of programmed cell death or apoptosis [41]. The activation of NFκB enhances the expression of genes encoding cytokines (e.g. TNF-α, IL-1, IL-6, IL-2, IL-12, INF-γ and CM-CSF), cell adhesion molecules (CAMs), chemokine receptors and other inducible enzymes (e.g. COX-2, iNOS) [42-44]. Figure 3 shows the TNF-α mediated inflammation and apoptosis in diabetes.

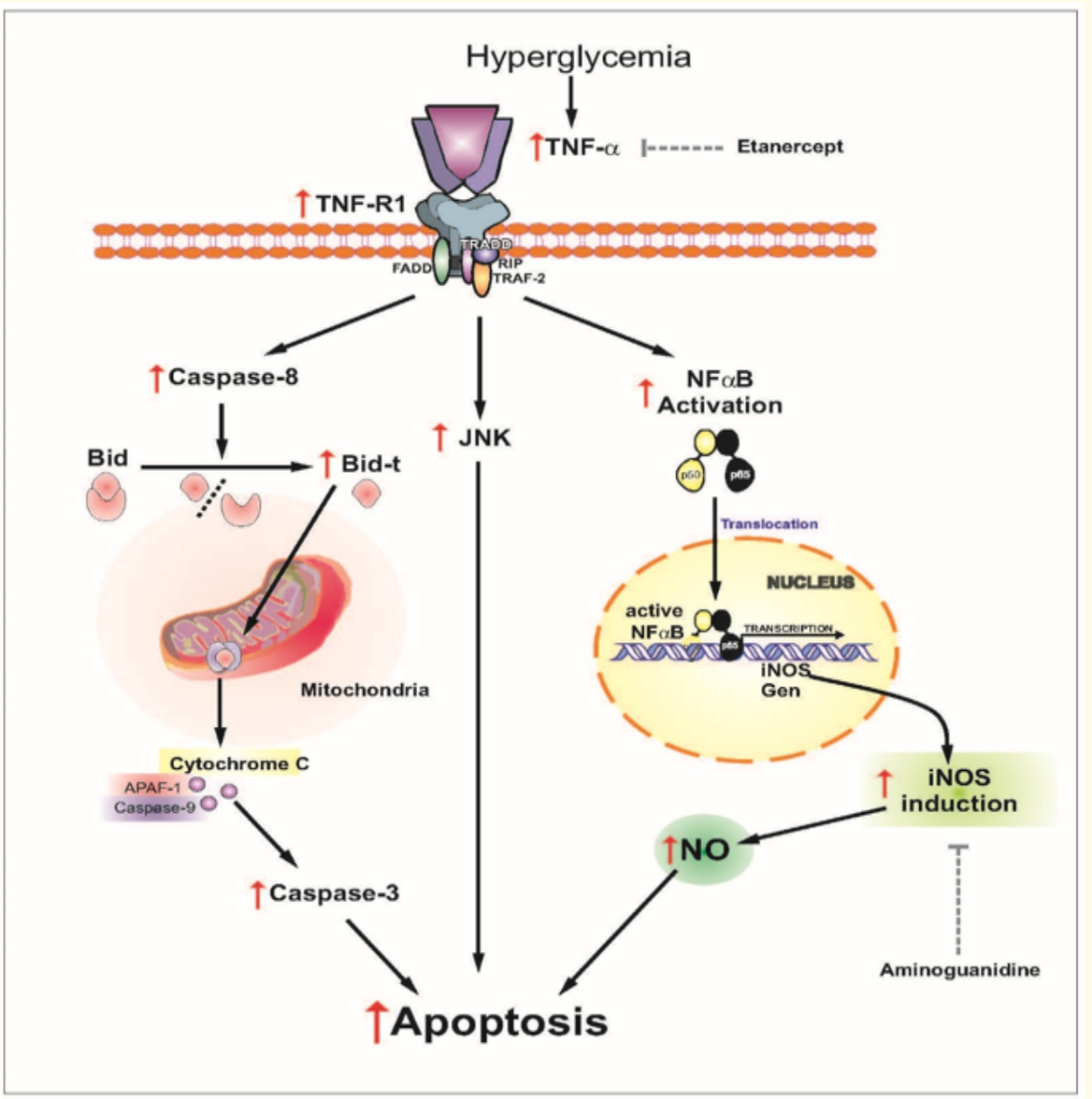

Figure 3: *TNF-α mediated inflammation and apoptosis in diabetes (Zimmermann et al., 2001).*

Particulars	Males	Female	Total
Diabetes	7.9%	7.5%	7.8%
Overweight	19.0%	23.9%	21.4%
Obesity	3.1%	6.5%	4.7%
Physical inactivity	9.2%	15.1%	12.15%

Table 2: *Prevalence of diabetes and related risk factors.*

Conclusions

The present review was structured to provide a concise information on diabetes and its complications, like hyperglycemia induced oxidative stress, inflammation and apoptosis. Researchers must focus on compounds that target overall complications associated with diabetes and also concentrate on improving the overall well-being of the diabetic patients.

Conflict of Interest

All authors declare that there were no conflicts of interest concerning this publication.

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