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Review

Chronic hyperglycemia mediated physiological alteration and metabolic distortion leads to organ dysfunction, infection, cancer progression and other pathophysiological consequences: An update on glucose toxicity

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ABSTRACT

Chronic exposure of glucose rich environment creates several physiological and pathophysiological changes. There are several pathways by which hyperglycemia exacerbate its toxic effect on cells, tissues and organ systems. Hyperglycemia can induce oxidative stress, upsurge polyol pathway, activate protein kinase C (PKC), enhance hexosamine biosynthetic pathway (HBP), promote the formation of advanced glycation end-products (AGEs) and finally alters gene expressions. Prolonged hyperglycemic condition leads to severe diabetic condition by damaging the pancreatic β-cell and inducing insulin resistance. Numerous complications have been associated with diabetes, thus it has become a major health issue in the 21st century and has received serious attention. Dysregulation in the cardiovascular and reproductive systems along with nephropathy, retinopathy, neuropathy, diabetic foot ulcer may arise in the advanced stages of diabetes. High glucose level also encourages proliferation of cancer cells, development of osteoarthritis and potentiates a suitable environment for infections. This review culminates how elevated glucose level carries out its toxicity in cells, metabolic distortion along with organ dysfunction and elucidates the complications associated with chronic hyperglycemia.

1. Introduction

Glucose is the primary fuel for cells. It serves as an energy provider accompanied by precursors for several biosynthetic pathways. Intake of glucose in insulin-dependent tissues like adipose tissues and muscles is mediated through GLUT4, glucose transporter protein. GLUT1, the other transporter is insulin-independent and widely expressed in most of the tissues. The requirement of glucose is essential for every cell and they can utilize that glucose according to their specific functions. GLUT1, the major transporter protein of brain cells, can uptake glucose at a low concentration without the assistance of insulin. GLUT4 has a high K_M for glucose and thus after taking a meal, when the glucose level is elevated, the adipose tissues and muscles also become active for consuming extra glucose for storage as glycogen [1]. Insulin, secreted by pancreas plays a key role in glucose homeostasis. Insulin augments glycolysis, glycogenesis, lipogenesis, and protein synthesis and decreases gluconeogenesis. Insulin resistance or impaired effects of insulin in target tissues is induced by hyperglycemia, inflammation, obesity

Abbreviations: AGEs, advanced glycation end-products; CAD, coronary artery disease; CRP C, reactive protein; CTGF, connective tissue growth factor; DAG, diacyl glycerol; DCM, diabetic cardio-myopathy; DFU, diabetic foot ulcer; eNOS, endothelial nitric oxide synthase; FOXO1, forkhead box O1; GBM, glomerular basement membrane; GDNF, glial cell line derived neurotrophic factor; GLUT, glucose transporter protein; HBP, hexosamine biosynthetic pathway; HIF, hypoxia-inducible factor; HNE, 4-hydroxynoneal; ICAM, intercellular adhesion molecule; IGF-1, insulin like growth factor-1; IL-6, interleukin-6; IRS, insulin receptor substrate; LHP, lipid hydroperoxides; MAPK, mitogen activated protein kinase; MCP-1, monocyte chemo attractant protein -1; MDA, malonaldehyde; MGO, methyl-glyoxal; MI, myocardial infarction; MMPs, matrix-metalloproteinase; NAFLD, non-alcoholic fatty liver; NEFA, non essential fatty acid; NOX2, NADPH oxidase; OGG1-8-oxo, G DNA glycosylase; PARP, poly-ADP-ribose polymerase; PDGF, platelet derived growth factor; PDX-1, pancreatic duodenal homebox-1; PKC, protein kinase C; RAGE, receptor for advanced glycation end-products; RD, reproductive dysfunction; RET, receptor tyrosine kinase; ROS, reactive oxygen species; SDF-1, stromal cell-derived factor-1; SGLT, sodium glucose co-transporter; SIR, standardized incidence ratio; TGF- β, transforming growth factor- β; TNF α, tumor necrosis factor- α; Txnip, thioredoxin-interacting protein; UCP, uncoupling protein; UPR, unfolded protein response; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor

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and other factors [2]. When insulin resistance in peripheral tissues occurs, the pancreas produces more insulin for overcoming such conditions. When the β-cells fail to compensate this stress, apoptotic cell death occurs leading to a defect in insulin production and secretion. This consequence elevates the level of blood glucose gradually and develops hyperglycemia. Chronic hyperglycemia mediates irreversible cell damage, referred as glucose toxicity [3]. Prolonged hyperglycemia results in the onset of diabetes mellitus. The effect of glucose toxicity mainly occurs in capillary endothelial cells of retina, mesangial cells of the renal glomerulus, neurons and Schwann cells of peripheral nerves causing retinopathy, nephropathy, and neuropathy [4]. In addition to these complications, elevated blood glucose level has been a potent activator in developing cardiovascular diseases, cell proliferation and progression of cancer cells, mediating inflammation in osteoarthritis.

The present review will address the homeostasis of glucose, glucose toxicity and the effect of glucose toxicity on cells. This review will also focus on diabetes mellitus and other complications related with diabetes mellitus. Role of hyperglycemia on several diseases will also be enlightened in our approach.

2. Glucose as fuel or precursors

Glucose, a simple form of carbohydrate, is readily utilized by the body for providing instant energy. Constant supply of glucose is required for a source of energy especially for the brain and erythrocytes. Under normal physiological conditions, most of the glucose is consumed by glycolysis and the remaining portion is used by the pentose phosphate pathway [5]. In the liver, about 30% of the glucose gets oxidized via pentose phosphate pathway. Rapidly proliferating cells utilize pentose phosphate pathway for ribose as well as NADPH. In cells, glucose not only serves as a source of energy production but also plays a key role in different biosynthetic pathways. Glucose is readily converted to glycogen, stored in the liver and muscles and thus removes the extra blood glucose load after a meal. In adipose tissues, glucose is required for the generation of glycerol. In addition, glucose can be oxidized to glucuronic acid, used in the detoxication and formation of muco-polysaccharides through uronic acid pathways. It can also be reduced into sorbitol, normally present in the lens of eyes. Glucose not only provides energy in the brain but also serves as a precursor for the biosynthesis of neurotransmitters [6]. As brain cannot store glucose, constant supply of glucose is always required for its proper functioning [7].

3. Glucose homeostasis

In humans, the normal blood glucose level is 70–110 mg/dL and is tightly regulated by maintaining the balance between the sources of glucose in blood (diet, glycogenolysis, gluconeogenesis) and the removal of glucose from blood (glycolysis, glycogenesis, lipogenesis, uronic acid pathway etc.) through precisely hormonal regulation. This makes the blood glucose level maintained at a steady-state condition, called glucose homeostasis. However, the glucose level can vary throughout the day. Glucose levels generally remain low in the morning whereas rises after taking a meal.

3.1. Defects in glucose homeostasis

3.1.1. Hypoglycemia

When the blood glucose level becomes lower than 50 mg/dL, it is called hypoglycemia [8]. It may cause loss of consciousness, coma and even death. Hypoglycemia may occur when the insulin concentration is high or due to low food intake or after over exercise [9]. A patient with diabetes under insulin treatment along with the patient with pancreatic beta cell tumor or insulinoma may face such hypoglycemic shock.

3.1.2. Hyperglycemia

Hyperglycemia indicates high blood sugar level for longer periods. When the blood glucose level is higher than 90–130 mg/dL after fasting for at least 8 h, it indicates that fasting hyperglycemia and postprandial hyperglycemia occurs when the blood glucose level is more than 180 mg/dL after taking a meal [10]. According to American Diabetes Association guidelines, if the blood glucose level exists between 100–126 mg/dL (around 5.6–around 7 mmol/l), it is regarded as hyperglycemic. When the blood glucose level is greater than7 mmol/L, it is considered to be diabetic. Chronic hyperglycemia is one of the major cause of organ damage.

Glucose toxicity is the result of several devastating effects of persistent hyperglycemia on different cell types [11]. Numerous studies have identified the molecular mechanisms of hyperglycemia and its consequences [11–13]. Hyperglycemia exerts ROS production and DNA damage [14,15], suggesting a role in developing an inflammatory response [16]. Hyperglycemia has been shown to stimulate polyol pathway and hexosamine pathway. Other factors that may contribute in causing hyperglycemia includes advanced glycation, end products (AGEs) formation and protein kinase C (PKC) activation [17]. Reduced insulin sensitivity has been observed under glucose exposed primary rat adipocytes [18]. It has also been demonstrated that hyperglycemia-induced insulin resistance is not readily reversible [16]. Hyperglycemia exerts its toxicity on different biomolecules (proteins, DNA) organelles and cells. It is well accepted that hyperglycemia has also been implicated in developing micro and macrovascular complications in diabetes [19]. Late complications of diabetes includes nephropathy, retinopathy, neuropathy, atherosclerosis, infection prone condition [13]. In addition, other associated complications may include hypothyroidism, hyperthyroidism, non-alcoholic fatty liver disease, limited joint mobility, edema [20].

3.1.3. Glucose toxicity

Glucose toxicity of the islets may be defined as irreversible β-cell damage by prolonged exposure of high glucose concentration (hyperglycemia) [21]. It also contributes to development of insulin resistance and dysfunction of insulin secretion. Furthermore, glucose toxicity also lowers the translation rate in insulin synthesis, inhibition of glucokinase gene expression, impaired mitochondrial function [22,23]. General mechanisms of glucose toxicity includes enhancing oxidative stress, stimulation of polyol pathway, PKC activation, stimulation of hexosamine biosynthetic pathway (HBP), AGEs formation and changes in gene expression [5,11] (Fig. 1).

3.1.4. Glucose toxicity & oxidative stress

Oxidative stress may be defined as a disturbance in the balance between the formation of pro-oxidants and impaired action of the antioxidant system [13]. Under normal conditions, redox balance is maintained through the generation of free radicals by cellular metabolism and their removal by the antioxidant system. Hyperglycemia has been implicated as a stimulator of oxidative stress [24,25]. Overproduction of electron donors such as NADH and $FADH_2$ occurs due to the oxidation of the excess amount of glucose through glycolysis and Krebs cycle, resulting in the enhancement of ATP/ADP ratio and alteration of the mitochondrial membrane potential. High proton gradient creates more electrochemical potential difference which diminishes the electron transport machinery in complex III resulting in the accumulation of electrons in coenzyme Q. This leads to the generation of free radical superoxide, which can be converted to another form of ROS including peroxynitrite ($ONOO^-$), hydroxyl (·OH) and hydrogen peroxide (H_2O_2). Peroxisome is another source for ROS generation apart from mitochondria in the cell. It has been proposed that the generation of ROS play a critical role in mitochondrial dysfunction and mitochondrial stress which has a significant role in diabetes. Thus, elevated level of $NADH/NAD^+$ leads to the generation of oxidative stress [17,26,27]. Under hyperglycemic conditions,