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AN OVERVIEW OF CLASSICAL & NON-CLASSICAL DIABETIC COMPLICATIONS & ITS UNDERLYING MECHANISM

Praveen Kumar Soni [1 & 2*], Ashish Agrawal [3]

1. PhD Research Scholar, Faculty of Pharmacy, Mandsaur University, Mandsaur, 458001
2. School of Pharmacy, Sangam University, Bhilwara, Rajasthan, 311802
3. Faculty of Pharmacy, Mandsaur University, Mandsaur, 458001

ABSTRACT

Many endothelial capillary cells are damaged under these conditions, including those in the retina, renal glomerulus, and both central and peripheral nerves, due to excessive harmful accumulation of glucose in these cells. Elevated blood glucose levels or HG increase aldose reductase activity that converts glucose to sorbitol. Intracellular sorbitol accumulation increases cellular osmotic injury, and exaggerates oxidative stress. Sorbitol dehydrogenase eventually converts sorbitol to fructose. During prolonged increases in blood glucose levels, the PKC pathway is an added element in diabetic complications. Hyperglycaemia induces the production of diacylglycerol, which promotes activation of the PKC pathway. People with mild and severe chronic DM have to comply with daily intake of hypoglycemic drugs, including insulin, and they must also exercise every day. Adherence to both non-pharmacological and pharmacological treatments, as well as knowledge about DM can definitely improve the quality of life of diabetic patients.

KEYWORDS-

Classical & Non-Classical, Diabetic Complications, Underlying Mechanism, Hyperglycaemia, Sorbitol dehydrogenase.

INTRODUCTION

Diabetic complications associated with hyperglycaemia (HG) impair the metabolism of carbohydrates, fats, proteins and electrolytes, all of which can disrupt the vascular system [1]. Many endothelial capillary cells are damaged under these conditions, including those in the retina, renal glomeru- lus, and both central and peripheral nerves, due to excessive harmful accumulation of glucose in these cells [2]. The criti- cal mechanisms

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involved in the development of diabetic complications are mainly induced by chronic HG, impaired lipid catabolism, exaggerated production of reactive oxygen species (ROS) and a reduced antioxidant protective system, that all lead to insulin-resistance and increased damage of beta-cells in the pancreas [3]. Herewith shows a few of the long-term complications of diabetes associated with HG in different tissues and organ systems.

A. The Polyol Pathway

Essential enzymes in the polyol pathway include aldose reductase and sorbitol dehydrogenase. Elevated blood glucose levels or HG increase aldose reductase activity that converts glucose to sorbitol. Intracellular sorbitol accumulation increases cellular osmotic injury, and exaggerates oxida- tive stress. Sorbitol dehydrogenase eventually converts sorbitol to fructose [4]. Amplified action of both enzymes in the polyol pathway will deplete more of the NADPH needed for reformation of the reduced glutathione antioxidant co-factor, which in turn worsens the oxidative stress [2]. Furthermore, the Protein Kinase-C (PKC) pathway is stimulated under the influence of aldose reductase, via diacylglycerol production [5].

B. Increased Hexosamine Pathway Activity

When blood glucose level increases, the normal glycolysis pathway shifts to the hexosamine pathway. This, in turn, worsens diabetic complications and increases the burdens of oxidative stress via the production of excess uridine diphosphate-N-acetyl glucosamine (UDP-GlcNAc) [2]. The over-production of UDP-GlcNAc enhances O-glycosylation of the transcription factor Sp1. A defective Sp1 will stimulate the productive of genes that play a role in the development of long-term complications of DM. In fact, elevated levels of UDP-GlcNAc are seen in tissues of diabetic subjects with severe long-term complications [6]. Increased SP1 glycosylation has also been shown to increase the tissue level of transforming growth factor-P1 (TGF-P1) and plasminogen activator inhibitor-1 (PAI-1), which in turn induces expression of some harmful genes responsible for the development of angiopathy [6]. Elevated expression of either PAI-1 or TGF-P1 leads to stimulation of vascular atherosclerosis, fibrosis and reduction of mesangial cell differentiation, respectively [7]. In addition to the hexosamine pathway, a dual effect by the PKC pathway occurs, resulting in an increase in the expression of PAI-1, which aggravates diabetic complications. Moreover, normal glucose metabolism is impaired in DM due to excess formation of N-Acetylglucosamine (GlcNAc) via the hexosamine

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pathway, promoting increased production of hydrogen peroxide, a free radical that can sup- press gene expression of glucose transporter 2, glucokinase and insulin [8].

C. Protein kinase-C Activation

During prolonged increases in blood glucose levels, the PKC pathway is an added element in diabetic complications. Hyperglycaemia induces the production of diacylglycerol, which promotes activation of the PKC pathway [9]. Stimulation of the PKC pathway worsens diabetic injuries via the overproduction of angiogenic proteins, such as vascular endothelial growth factor (VEGF), atherogenetic proteins, such as methylglyoxal (MGO), as well as other proteins, such as transforming growth factor-P1, fibronectin, nuclear factor- Kappa B, PAI-1 and other factors. PKC also promotes abnormal vascular permeability, hypoxia, induction of pro- inflammatory genes, and an increase in insulin- resistance with reduction of anti-atherosclerotic elements [10-15].

D. Increased Formation of Advanced Glycation-end Products

Chronically elevated intracellular glucose levels in DM can lead to an increase in the formation of reactive dicarbonyl species including methylglyoxal (MGO), which binds to protein molecules and produce advanced glycation- end products (AGEs) [9]. Accumulation of AGEs in cells disrupts their normal metabolic activities and alters gene expression of DNA. In addition, increased dispersal of AGEs to the extracellular matrix can impair cellular signaling, and may stimulate receptor-binding of AGEs [16, 17]. Exaggerated receptor-ligation of AGEs induces a greater expression of nuclear factor-Kappa B, which stimulates many cellular cascades involved in the production of inflammatory factors and markers including tumor necrosis factor (TNF) and different interleukins that ultimately lead to cell death [18, 19]. Furthermore, increased receptor-binding by AGEs worsens oxidative stress through overproduction of ROS [20].

CLASSICAL COMPLICATIONS OF DIABETES MELLITUS

A. Macrovascular Diabetes Complications

Hyperglycaemia (HG) is the main manifestation of DM, which in turn can impair the structure and function of many tissues in the body, especially the vascular system. As the HG becomes chronic with time, it can severely damage the vascular system via MGO

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and other mediators. Vascular complications in DM is classified into two categories, namely macrovascular, which includes coronary and peripheral arterial disease, and microvascular, which is associated with other DM-induced long-term complications such as neuropathy, retinopathy, nephropathy and in part, diabetic foot and cardiovascular diseases [36].

The endothelial cell impairments involved in macrovascular complications have many inducing elements, including elevated blood glucose levels, MGO, lipids, and inflammatory factors [37]. DM is also associated with excessive production of ROS, which in turn can induce vasoconstriction with accelerated lipid peroxidation and inflammatory reactions leading to atherosclerosis [38]. Atherosclerosis is a process of increased lipid deposition, especially low-density lipoprotein (LDL), in the sub-endothelial layer of large blood vessels. Atherosclerosis occurs more often in patients with DM as compared to patients without DM [39]. In addition to this, atherosclerosis increases the endothelial penetrability of blood vessels, which is prominent in DM [40]. The antioxidant and anti-inflammatory protective actions of high- density lipoprotein (HDL) are suppressed with increased inflammation due to excessive liberation of ROS, which induces oxidation of phospholipids and sterols [41]. Other macrovascular complications, such as calcification and plaque formation, can add to the development of severe vascular complications [42].

Diabetic Coronary Artery Disease

Coronary artery disease (CAD), stroke and peripheral arterial disease (PAD) are common in DM, leading to a high mortality rate among diabetic patients [9]. DM-induced cardiomyopathy is mainly associated with dyslipidaemia and increased blood pressure. Development of prominent cardiac fibrosis associated with cardiomyopathy is further enhanced by overproduction of oxidative free radicals that disrupt myocardial cells, leading to dysregulation of cellular calcium homeostasis, contractile dysfunction, remodelling of the myocardium and subsequently, death of cardiomyocytes. Oxidative stress inhibits the antioxidant protective system in diabetic patients [43].

B. Microvascular Diabetic Complications

On the other hand, diabetic microvascular complications are mainly associated with impairment of vascular permeability that affects different tissues and organs of the body

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including the kidneys, retina and nerves [44]. Chronic, un- treated and prolonged HG can further cause vascular permeability, disruption of glycocalyx structure, increase in water and protein retention, resulting in generalized edema [40]. At the same time, PKC is elevated in DM-induced HG leading to an increased vascular permeability via an elevation of extracellular fluids and apoptosis of angiogenic cells [15].

Vascular endothelial growth factor (VEGF) is an impor- tant element in tissue neogenesis and vascular healing. How- ever, VEGF has also an initiatory destructive role in microvascular diabetic complications [45]. VEGF can directly influence glomerular permeability as well [46, 47]. Although suppression of VEGF slows the development of proliferative diabetic retinopathy [48], VEGF-inhibition can also lead to an increase in DM-induced hypertension and glomerular proteinuria, with diminished vascular wound healing [49,50].

Diabetic Nephropathy

Diabetic nephropathy is associated with morphological impairment of the glomerular endothelial cell barrier [51] and the glomerular basement membrane. This, in turn, leads to an elevation of protein filtration in urine, reflecting disturbed protein degradation in the diabetic patient [52]. Oxidative stress progression in DM can induce gene expression of angiotensinogen, leading to renal function impairment [53, 54]. Diabetic nephropathy is a disease that patients can genetically be susceptible to, but can also be induced by certain environmental insults [55]. Approximately one-third of all uncontrolled diabetic patients will suffer from diabetic nephropathy ending with renal dialysis. This can either be due to the previously mentioned genetic susceptibility and/or the reaction of cytokines with reactive oxygen species or advanced glycation end products. The early indicator of diabetic nephropathy is increased urinary albumin excretion [56].

Diabetic Retinopathy

In numerous cases, DM is indirectly diagnosed via an eye test for impaired vision. If left untreated, DM can lead to blindness. Risk of blindness in diabetic subjects is associated with prolonged incidence of retinopathy, which in most patients is usually revealed to have been going on for decades, with the risk of losing vision increasing in time [57]. HG can induce diabetic retinopathy through stimulation of PKC. The activation of PKC can result in elevation of many metabolic pathways, stimulation of cell growth and

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apoptosis, and increase in cellular permeability. Changes in these processes are associated with the progression of different diabetes- induced vascular complications, including cardiomyopathy, atherosclerosis, neuropathy, nephropathy and retinopathy [58]. In addition, HG and states of oxidative stress associated with diabetic retinopathy also stimulate certain apoptotic growth factors that may contribute to diabetic cataract formation [4, 59]. Furthermore, the elevated glucose level in retinal cells of diabetic individuals may lead to increased risk of retinopathy and accompanying blindness [60, 61]. Moreover, elevated levels of ROS due to provoked oxidative stress can lead to an increase in lipid peroxidation, and a concomitant impairment of the antioxidant protective system, all of which prompt DNA injury in the retina of diabetic patients [2, 57, 62].

C. Diabetic Neuropathy

The progression of diabetic neuropathic complications is highly accelerated after prolonged years of HG [10]. Chronic HG may lead to either sensory or motor neuropathic problems or autonomic nervous system dysfunction, including arrhythmias, gastroparesis, incontinence and sexual dysfunction [63]. However, patients with long-term diabetes may have one or more types of neuropathies.

Peripheral Neuropathy

Diabetic peripheral neuropathy is one of the major com- plications affecting patients with DM. This can lead to either sensory or sensorimotor neuropathies that increase the risk of foot ulceration and amputation in some cases of uncontrolled diabetic patients [64]. Chronically elevated blood glucose levels and the resulting activated polyol pathway, with reduced blood supply to endoneurial tissues, are all associated with reduced protective nitric oxide formation and Na^+/K^+-ATPase dysfunction [7]. Concurrently, neural cell regeneration is severely reduced due to an inhibition of insulin-like- growth factor [65]. An increased activation of the polyol pathway diminishes NADPH, which is otherwise required for activation of glutathione reductase, aldose reductase and endothelial nitric oxide synthase. This all leads to worsening of oxidative stress and acceleration of neurodegradation. Moreover, elevation of intraneural sorbitol can induce nerve cell necrosis and subsequently, cellular degradation [10, 66]. Glycation of proteins within nerves in patients with DM [67], destabilizes the cytoskeleton, and contributes to slowing of axonal transport and nerve impulses while accelerating nerve

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degeneration [68].

Autonomic Neuropathy

a. Diabetes and Gastrointestinal Dysfunction

Autonomic neuropathy may cause abnormal function of the digestive system. Diabetic patients with autonomic neuropathy may complain of symptoms such as early satiety, bloating, nausea, vomiting, abdominal pain and heartburn. Slowed stomach emptying, or gastroparesis, is usually detected in diabetic patients with prolonged HG. Diabetic enteropathy also leads to acid reflux disease, delayed bowel movement, constipation, diarrhoea, and increased rate of bacterial, viral and fungal gastrointestinal tract infections. Furthermore, diabetes-induced HG is associated with salivary and exocrine pancreatic insufficiencies due to a reduction in the synthesis and secretion of amylase, an important digestive enzyme responsible for the breakdown of carbohydrates [69, 70].

Diabetes and Erectile Dysfunction

Erectile dysfunction is a common complication of DM, and is mainly related to disturbed communication between vascular and neuronal systems due to either weakened blood circulation in penile tissue or impairment of neuronal stimulation [71]. In addition to the vascular and neuronal disturbance related to erectile dysfunction in diabetic patients, there are other elements involved, including hormonal changes, chronic diseases, malnutrition, penile tissue infection and psychological influences [72]. Impotence related to DM is much more frequent in diabetic than in non-diabetic men [73]. Increased free radicals, such as malondialdehyde, are believed to disrupt the neuronal and vascular activities controlling penile erection [74]. Impaired ejaculation and diminished satisfaction are other symptoms that diabetic patients may encounter [75].

D. Diabetic Foot and Wound Healing

Diabetic foot occurs as an interplay of abnormal structure and function of blood vessels and nerves leading to reduced angiogenesis [76], loss of sensation, unhealed secondary wound infections, ulceration and subsequently foot amputation [77]. Diabetic foot ulceration is mainly due to neuropathy and ischemia occurring together. Diabetic foot is associated with increased incidence of foot trauma due to decreased proprioception. The underlying ischemia results in impaired wound-healing in the injured area(s), and superimposed infections lead to ulceration [78]. The symptoms of diabetic

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neuropathic foot include but not limited to numbness and tingling sensation, pain that may be sharp in nature and sensitivity to touch. Neuropathic diabetic foot also has reduced pain sensation [79]. Diabetic foot is associated with morbidity because of leg amputation [80]. Persistently un- successful wound-healing in diabetic foot syndrome can also occur even with sufficient medical therapy [81]. Prolonged, non-healing foot ulcers are a ground for foot amputation [82]. All stages of the complex wound-healing cascade are impaired in DM and compounded by many factors including inflammation, proliferation, angiogenesis, apoptosis, reduced chemotaxis and matrix formation, diminished bacterial resistance, and deterioration of the antioxidant protective system. All of these lead to failure of wound-healing [83]. Also, peripheral vascular disease is prevalent in the legs of patients with uncontrolled diabetes due to atherosclerosis that may ultimately lead to foot amputation [3].

NON-CLASSICAL CHRONIC COMPLICATIONS

A. Periodontal Disease

DM can be diagnosed through dental examination due to diabetic complications affecting the oral cavity. Impairment of the immune system in diabetic patients enhances the development of periodontal disease due to increased bacterial accumulation between teeth and gingiva, accelerating gum infection and promoting bone demolition. Chronic periodontitis can lead to gum retraction, swelling, bleeding, fetor ex ore and tooth loss. Diabetic patients also experience salivary insufficiency, which is associated with a reduction in salivary amylase and fluid secretion [84].

B. Diabetic Bone Diseases

Impairment of insulin-secretion, which is associated with type 1 diabetes, can lead to diminished bone mineral density with an elevated bone fracture rate [85, 86]. An exaggerated production of glycation-end products in DM is associated with the progression of diabetic complications including microangiopathy and atherosclerosis, which can also lead to diabetic bone disease [87].

C. Diabetes and Skin Disorders

Manifestations of diabetes can also involve the skin. Chronic dermal infections are due to increased blood glucose supply to the skin. The HG in turn increases the occurrence of bacterial and fungal infections, leading to pruritus and other symptoms of skin disease. In addition to HG, increased accumulation of subcutaneous adipose

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tissue related to obesity stimulates colonization and growth of Candida albicans. Also, skin dehydration may lead to changes in the normal dermal flora, and give way to colonization by pathogenic bacteria. Furthermore, DM is associated with delayed wound-healing [88] as discussed in earlier section.

OTHER CONDITIONS THAT MAY BE ASSOCIATED

A. Hypertension

It is now known that DM is a major risk factor in the development of hypertension. Moreover, diabetes-induced hypertension is one of the influencing causes of cardiovascular disease, including heart failure and other long-term complications, such as retinopathy, nephropathy and cerebrovascular accidents [36]. There is extensive evidence showing that controlling hypertension in DM can significantly diminish these diabetic complications [89]. End-stage renal disease is mainly associated with increased hypertension in DM, HG and glycated haemoglobin, all of which can lead to microalbuminuria due to reduced glomerular filtration [90].

B. Obesity

Obesity is a leading risk factor for many chronic diseases including insulin-resistance, type 2 DM, gastroesophageal reflux, hypertension, dyslipidemia, cardiovascular diseases and certain types of cancers [91]. Obesity can develop due to modern lifestyle habits such as excessive food intake, reduced physical activity, environmental factors, psychological effects and genetic susceptibility, which all have an effect on general health and mortality [92]. Increased body weight can also be related to hormonal and neuronal disturbances [93].

In addition to the harmful effect of HG on the progression of cardiovascular diseases, increased levels of cholesterol, LDL, total cholesterol, triglycerides and low level of HDL cholesterol may contribute to the development of heart disease in diabetic patients [94]. Obesity in children also increases the risk of insulin-resistance, disturbed lipid metabolism and hypertension [95]. Moreover, obesity hastens the ageing process, reduces the quality of life and increases morbidity and mortality even at an early age in life [96].

CONTROLLING DIABETIC COMPLICATIONS

There is now sufficient evidence that diabetes can cause many of the complications that have been outlined in this mini review. It is particularly noteworthy that diabetes is

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associated with ageing, and millions of people in the world are diabetic. People should endeavor to keep their blood glucose values at or close to the normal levels. This can be done via both pharmacological and/or non-pharmacological interventions involving daily exercise of 30 min per day or 3 hours per week. People with mild and severe chronic DM have to comply with daily intake of hypoglycemic drugs, including insulin, and they must also exercise every day. Adherence to both non-pharmacological and pharmacological treatments, as well as knowledge about DM can definitely improve the quality of life of diabetic patients.

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