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DIABETES MELLITUS AND MECHANISM OF CHRONIC COMPLICATIONS: REVIEW ARTICLE

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ABSTRACT

Diabetes mellitus (DM) is comprises a group of common metabolic disorders that share the phenotype of hyperglycemia. Complex interaction of genetics, environmental factors and sedentary lifestyle are responsible for its development. Metabolic derangement related with DM induces secondary pathophysiologic changes in multiple organ systems which impose a tremendous burden on the individual with diabetes and the health care system of the country. Worldwide 415 million adults have diabetes and this will rise to 642 million by 2040. In chronic stage DM affects many organ systems, and its complications increase the risk for morbidity and mortality. Many physiological impairments including platelet hyper-reactivity, a tendency for negative arterial remodeling, impaired fibrinolysis coupled with a tendency for thrombosis and coagulation, increased inflammation, and endothelial dysfunction, increases the risk of atherosclerotic vascular disease and other chronic complications like retinopathy, neuropathy. Among these, endothelial dysfunction is an important responsible factor for these pathological manifestations. Various mechanisms have been described for endothelial dysfunction in DM but, most likely are metabolic derangements such as hyperglycemia, excess liberation of free fatty acids (FFAs), and insulin resistance. Additional to these oxidative stress induced reactive oxygen species; inflammation and thrombosis also accentuate endothelial dysfunction. This review article describes mechanism associated with chronic complications of DM in brief.

KEYWORDS: Diabetes mellitus, chronic complications, metabolic derangement, endothelial dysfunction.

INTRODUCTION

Diabetes mellitus (DM) is comprises a group of common metabolic disorders that share the phenotype of hyperglycemia. Complex interaction of genetics, environmental factors and sedentary lifestyle are responsible for the development of DM. Factors contributing to hyperglycemia may include reduced insulin secretion, decreased glucose utilization, and reduced insulin sensitivity. The metabolic derangement associated with DM causes secondary pathophysiologic changes in multiple organ systems that increases burden on the individual with diabetes and on the health care system of the country. With an increasing incidence worldwide, DM will be a leading cause of morbidity and mortality in future.

The country with the greatest number of individuals with diabetes in 2015 are China (109.6 million) followed by India (69.2 million). Worldwide 415 million adults have diabetes; this will rise to 642 million by 2040.[60] The obesity accompanying DM, particularly in a central or visceral location, is thought to be part of the pathogenic process. The incidence of DM is greatly increased by the combination of obesity and a positive family history of diabetes. India is at third position after USA and China.[1]

Chronic complications of DM

DM in chronic stage affects many organ systems and its complications are responsible for the majority of morbidity and mortality associated with the disease. Chronic complications can be divided into vascular complications including microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (coronary artery disease, peripheral arterial disease, cerebrovascular disease) and nonvascular complications including gastroparesis, infections, and skin changes. The risk of chronic complications are more if the duration of hyperglycemia is longer; they usually become apparent in the second decade of hyperglycemia. Since DM often has a long asymptomatic hyperglycemic

period, most of the patients presents with complications at the time of diagnosis. Chronic hyperglycemia is responsible for the microvascular complications in both type 1 and 2 DM.

Large, randomized clinical trials of type 1 or type 2 DM have conclusively demonstrated that a reduction in plasma glucose concentration prevents or delays retinopathy, neuropathy and nephropathy. Other incompletely defined factors such as genetic susceptibility may modulate the development of complications. For example, despite long-standing DM, some individuals never develop nephropathy or retinopathy due to their different genetic makeup. The causative role of chronic hyperglycemia in the development of macrovascular complications is less conclusive. However, coronary heart disease and stroke events are greater in patients with DM. These events correlate with fasting and postprandial plasma glucose levels. Other factors (dyslipidemia and hypertension) also play important roles in macrovascular complications.

Mechanisms of complications

Chronic hyperglycemia is one of the important etiologic factor of complications of DM, but the mechanism(s) by which it leads to cellular and organ dysfunction is unknown. Four theories, which are not mutually exclusive, have been proposed to explain how hyperglycemia associated with chronic complications of DM (Figure 1).There are many physiological impairments that plausibly link DM with a marked increase in atherosclerotic vascular disease, including platelet hyper-reactivity, a tendency for negative arterial remodeling, impaired fibrinolysis coupled with a tendency for thrombosis and coagulation, increased inflammation, and endothelial dysfunction.[2,3] Of them, endothelial dysfunction may be an important factor responsible for these pathological manifestations.

Role of vascular endothelium

Vascular endothelium is the crucial regulator of vascular homeostasis and plays an important role in the control of:

- Vascular tone and blood flow
- Coagulation and thrombosis
- Nutrient delivery and waste removal
- Inflammation
- Vascular smooth muscle cell growth and migration
- Leukocyte attraction and diapedesis.

The endothelial dysfunction may create an environment that allows the development of vascular disease, providing a link between DM and microvascular and macrovascular disease (eg. retinopathy, nephropathy, MI, stroke, and amputation). The endothelium maintains a balance between vasodilatation and vasoconstriction, coagulation and anticoagulation, and leukocyte attraction and diapedesis. Among the factors regulated by the endothelium, perhaps the best characterized is nitric oxide (NO).[4] Produced by inducible nitric oxide synthase (iNOS) or endothelial NOS (eNOS), NO is a potent vasodilator, platelet antagonist, and anti-inflammatory agent.[6] Other important endothelium-elaborated mediators of vascular tone and function include endothelin and angiotensin II. In patients with high risk factor of vascular disease, such as DM or atherosclerosis *per se*, bioavailability of NO is attenuated. Thus, stimuli that commonly cause the release of NO are no longer able to produce vigorous vasodilatation. Infusion of acetylcholine or one of its congeners – methacholine, bradykinin, serotonin, or substance P may stimulate endothelial NOS (eNOS) and modulate release of NO.[7] This method is typically used to examine the resistance in arteriolar function. In peripheral vessels, NO bioavailability can be studied by the response to reactive hyperemia.[8] In this experimental model, a sphygmomanometric cuff is applied on the arm and inflated to suprasystolic pressure for 5 minutes. Upon release, blood flow into the limb beyond the cuff increases 4- to 7-fold. This increase in blood flow and shear stress across the segment of interest causes the release of NO, dilating the artery 60 to 70 seconds after cuff release. Thus, the increase in size (diameter) of the artery at one minute after restoration of flow is an index of NO bioavailability.[9]

Mechanisms of endothelial dysfunction in DM

Various mechanisms have been described for endothelial dysfunction in DM but most likely are metabolic derangements such as hyperglycemia, excess release of free fatty acids (FFAs), and insulin resistance.

Hyperglycemia

The endothelium becomes rapidly dysfunctional as early as 6 hours, in healthy human subjects in response to hyperglycemia.[10,11] The rapidity indicates that the endothelium is an early indicator of hyperglycemia. It may convey these changes rapidly because of the persistent expression of glucose transporter 1 in endothelial cells despite ambient hyperglycemia.[12] Thus the glucose concentration in vascular endothelial cells will be same as that in the extracellular environment. In contrast, vascular smooth muscle cells maintain a normal intracellular glucose concentration by limiting glucose transport.[13]

The increased production of pathogenic reactive oxygen species (ROS), (e.g., superoxide anion), represents a central abnormality caused by hyperglycemia. In DM vascular endothelial cells becomes the primary source of vascular oxidative stress.[14]

DM creates a cascade, employing an ever increasing number of cellular components in the production of ROS:

- To begin with the mitochondria, hyperglycemia attenuates the electron donation for ATP generation, shifting the electron transport chain towards generation of superoxide anions.[15]

• Mitochondrial superoxide anion production activates protein kinase C and NAD (P) H oxidase, ultimately increasing the production of cytosolic superoxide anions.[16]
• Increased superoxide anions scavenge NO to form peroxynitrite, which oxidizes the eNOS co-factor, tetrahydrobiopterin and triggers the production of superoxide anion instead of NO by eNOS.[17]
• Extracellular production of superoxide anions also increases as a result of increased xanthine oxidase liberation (likely from the liver).[18,19,20]

Hyperglycemia also increases other sources of oxidative stress, including the intracellular production of advanced glycation end product (AGE) and activation of the endothelial receptor for AGE (RAGE).[21] AGEs per se can produce ROS and via activation of RAGE, increase intracellular enzymatic production of ROS.[22,23] Controlling glycemia eliminates activation of protein kinase C, thus implicating the importance of this pathway of activation in vivo [24, 25].

Increased free fatty acid concentration

FFA liberation from adipocytes also augments the oxidative stress burden and diminishes NO bioavailability [26]. Increased plasma FFA heightens oxidative stress by augmenting small, dense, oxidized low-density lipoprotein (LDL) [27], and by directly affecting the endothelium [28]. In the endothelium, FFA induces membrane translocation and activation of protein kinase C, increases endothelin-1 production, and increases superoxide anion production.[29,30,31] In humans, endothelial dysfunction produced by FFA has been demonstrated. Infusion of FFA to postprandial levels impairs endothelial function in a matter of hours and this impairment can be reversed with the infusion of an antioxidant.[32]

Insulin resistance

In most cases insulin resistance precedes hyperglycemia by years to decades and plays a key role in atherogenesis. It also precedes beta cell failure that produces overt hyperglycemia. Although exemplified by impaired skeletal muscle glucose uptake, insulin resistance also occurs in the liver, adipose tissue, and the endothelium. The extent of insulin resistance correlates both with glucose disposal and endothelium-dependent vasodilatation.[33] Although there is a clustering of cardiovascular risk factors (the metabolic syndrome) prior to DM onset, it is likely that insulin resistance contributes additively to vascular risk. This pathobiological link suggests that improvements in insulin resistance may result in improved endothelium-dependent vasodilatation. Support for this concept has been demonstrated in humans with the insulin-sensitizing agents, troglitazone and metformin.[31,34]

Endothelial dysfunction in DM

The metabolic disturbances in DM described above impair the endothelial cell activity and make the vascular environment more favourable for development of atherosclerosis.

Vasomotor function

Bioavailability of endothelium-derived NO is decreased by augmented production of ROS, especially superoxide anions. Superoxide anions scavenge NO to form peroxynitrite [11]. Endothelium-dependent, NO-mediated vasodilatation is attenuated in resistance and conduit vessels in patients with type 1 and type 2 diabetes[35, 36, 37], and oxidative stress inhibits the production of compensatory vasodilators (eg, prostacylin) to further limit vasorelaxation.[38]

Production of endothelin-1 and angiotensin II, the vasoconstrictor peptides; also increased in DM. A wide variety of insults in DM – including insulin resistance and hyperglycemia, increased oxidative stress, protein kinase C membrane translocation and activation.[39] and RAGE ligand-receptor interaction [40] – leads to increase endothelin production.[30, 31] Endothelin causes vascular smooth muscle contraction with an increase in vascular tone, stimulates angiotensin II production and vascular smooth muscle proliferation, and increases salt and water retention[41]

Inflammation

Inflammation is the fuel in the atherogenic process[42, 43] and is strongly linked to DM and insulin resistance [44, 45]. With the T-lymphocyte migration into the vascular intima, atherosclerosis is initiated [43]. These cells produce cytokines and chemokines and recruit monocytes and vascular smooth muscle cells into the nascent plaque. Endothelial dysfunction enhances each of these early atherogenic processes through activation of inflammatory transcription factors, such as nuclear factor kappa B (NF-kB).[46, 47, 48] These factors increase gene expression of proinflammatory cytokines. In the Third National Health and Nutrition Examination Survey (NHANES III), both glycemia and insulin resistance correlated directly with markers of inflammation, demonstrating a link between the dysmetabolism of DM and poor vascular outcomes.[49] Similarly, improvements in insulin resistance and glycemic control reduce inflammation.[50,51] Reductions in inflammation through medication[52] or by reducing visceral adiposity [53], improve endothelial function and soluble markers of endothelial cellular activation.

DM increases endothelial cell matrix metalloproteinase production, which decreases synthesis of vascular smooth muscle cell collagen.[54,55] As collagen diminishes and fibrous cap collagen of mature atherosclerotic plaque metabolizes, the risk of plaque rupture increases.

Thrombosis

Diabetic endothelial cells produce a powerful coagulant found in atherosclerotic lesions, the tissue factor.[56] Moreover, the dysfunctional endothelium has attenuated anticoagulation as well. Thrombomodulin expression (a

cell-surface based anticoagulant) is decreased, while production of plasminogen activator inhibitor-1 (a fibrinolytic antagonist) is increased. Platelet activation and aggregation is enhanced by reduced NO and prostacylin[57,58,59] The increase in coagulation and thrombosis potentiate thrombus formation after plaque rupture and make the development of arterial occlusion and clinical events more likely.

Thus, the DM impairs every homeostatic mechanism adapted by the endothelium to prevent the development of atherosclerosis. Investigations in humans with DM have made clear the importance of many of the pathogenic processes elucidated by basic science investigation. As our understanding of human vascular function progresses, new therapeutic strategies may be developed to reduce the cardiovascular risk suffered by patients with DM.

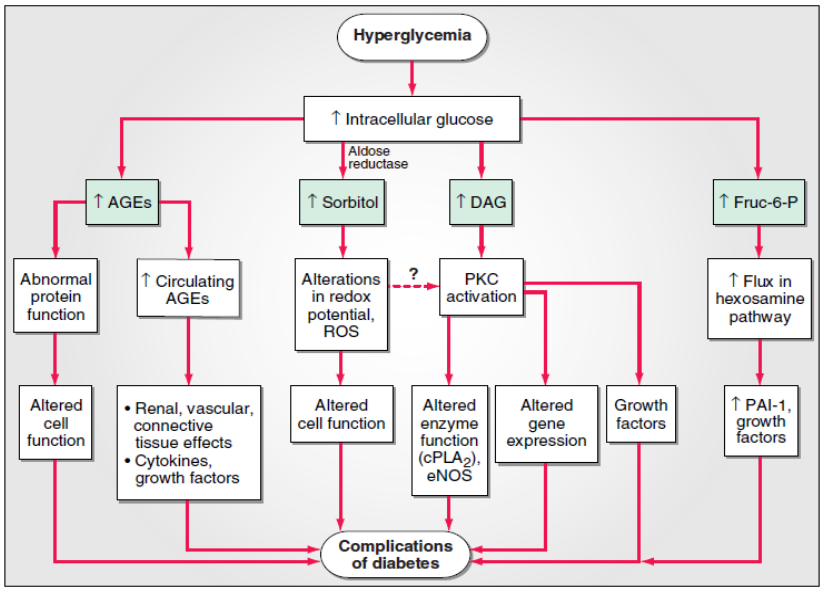

Figure 1: Possible molecular mechanisms of diabetes-related complications

[AGEs, advanced glycation end products; PKC, protein kinase C; DAG, diacylglycerol; cPLA2, phospholipase A2; eNOS, endothelial nitric oxide synthase; ROS, reactiveoxygen species; Fruc-6-P, fructose-6-phosphate; PAI-1, plasminogen activor inhibitor-1.].

Source

Modified from Harrison's Principles of Internal Medicine – 19th Ed. 2015, Mc Graw Hills, New Delhi.

CONCLUSION

Uncontrolled DM can lead to chronic complications which increases mortality and morbidity of individuals. It also increases economic burden of country. So, prompt diagnosis and treatment of DM is essential to prevent this sequel.

Conflict of Interest: non declared.

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