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Review Article

A Review: Effect of Diabetes on Vascular Endothelium

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ABSTRACT

Endothelial dysfunction is mainly observed in diabetics. The main role of endothelium is to control the tone of the vascular smooth muscle through the production of vasodilator mediators like nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF). Impaired endothelium-dependent vasodilation has been observed in vascular beds of different animal models of diabetes and in humans with type 1 and 2 diabetes. Hyperglycaemia causes repeated acute changes in intracellular metabolism and causes activation of polyol pathway, activation of protein kinase C, advanced glycation end product and increased oxidative stress.

Keywords: Diabetes, Endothelial dysfunction, Endothelium-derived hyperpolarizing factor

INTRODUCTION

Endothelial dysfunction plays a key role in the pathogenesis of diabetic vascular disease. The endothelium controls the tone of the underlying vascular smooth muscle through the production of vasodilator mediators. The endothelium-derived relaxing factors (EDRF) comprise nitric oxide (NO), prostacyclin, and a still elusive endothelium-derived hyperpolarizing factor (EDHF). Impaired endothelium-dependent vasodilation has been demonstrated in various vascular beds of different animal models of diabetes and in humans with type 1 and 2 diabetes. Loss of the modulatory role of the endothelium may be a critical and initiating factor in the development of diabetic vascular disease.[1] There are certain vascular effects observed due to vasoconstrictors and vasodilators.[2]

Table 1. Vascular Effects of Vasoconstrictors and Vasodilators

Vascular Effect	Vasoconstrictors*	Vasodilators#
Thrombosis	Increased	Decreased
Inflammation	Increased	Decreased
Oxidation	Increased	Decreased
Growth and migration of vascular smooth muscle cells	Increased	Decreased

* Includes angiotensin II, endothelin-1.
\# Includes nitric oxide, endothelial derived hyperpolarizing factors, natiuretic peptide, kinins.

Impaired endothelium - dependent vaso-dilatation may arise from several mechanisms: Decreased production of one of the EDRFs, Enhanced inactivation of EDRF, Impaired diffusion of EDRF to the underlying smooth muscle cells, Decreased responsiveness of the smooth muscle to EDRF and Enhanced generation of endothelium-derived constricting factors (EDCF).

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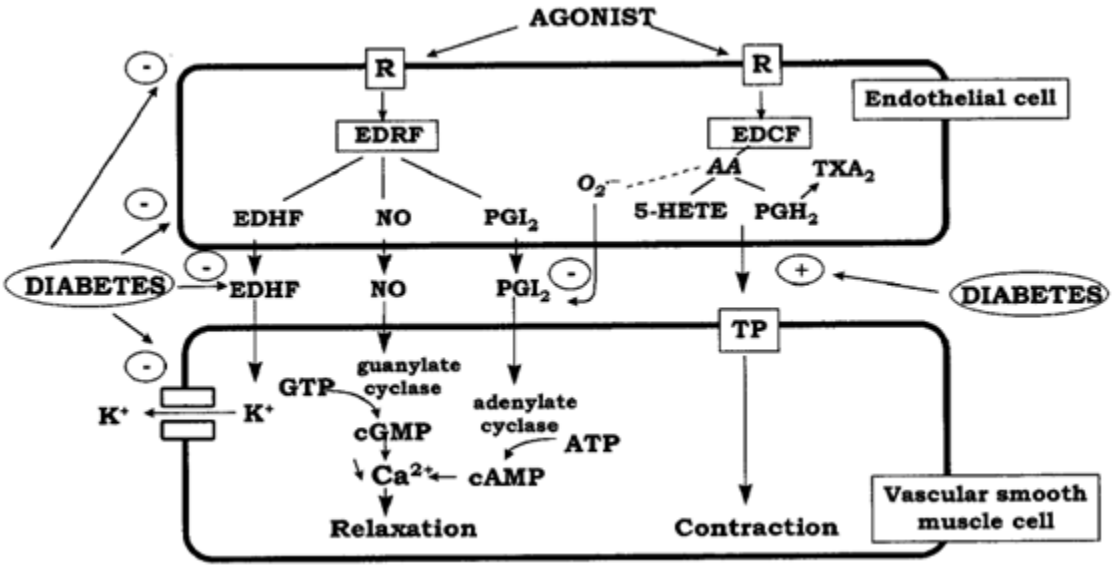

Fig 1. Mechanism of endothelial dysfunction in diabetes

Aetiology of endothelial dysfunction in diabetes

Hyperglycaemia induces repeated acute changes in intracellular metabolism (activation of polyol pathway, activation of diacylglycerol-protein kinase C, increased oxidative stress), as well as cumulative long-term changes in the structure and function of macromolecules through formation of advanced glycation end products (AGEs). The different pathways are discussed below.

Aldose reductase (Polyol Pathway)

Protein kinase C (PKC)

AGEs

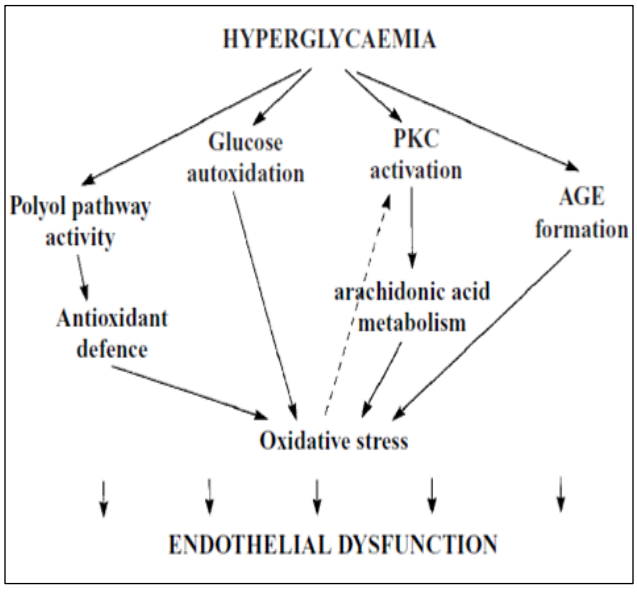

Fig 2. Outline and interactions of hyperglycaemia-induced metabolic pathways potentially involved in the pathophysiology ofendothelial dysfunction.

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1. Aldose reductase (Polyol Pathway):

In tissues that do not require insulin for cellular glucose uptake, such as the kidney, retina, nerves and blood vessels, hyperglycaemia activates the polyol pathway, resulting in the formation of sorbitol. Aldose reductase is the first and rate-limiting enzyme in the polyol pathway and reduces the aldehyde form of glucose to sorbitol. Glucose is reduced into sorbitol by aldose reductase, leading to depletion in NADPH. NADPH co-enzyme is essential for the regeneration of antioxidant molecules (reduced glutathione, ascorbate and tocopherol) and cofactor of eNOS. Aldose reductase inhibitors prevent the consumption of NADPH and energy in the polyol pathway and by virtue of this, may restore impaired EDRF production and endogenous antioxidant protection. So far, no studies have evaluated the potential beneficial effect of aldose reductase inhibitors on endothelial function in human diabetes.

Sorbitol is then oxidized to fructose by sorbitol dehydrogenase enzyme. This reaction uses NAD+ and raises the NADH/NAD+ ratio modifying the redox state of the cells, and leading to the production of superoxide anions. Several studies suggest that abnormalities such as vascular permeability and flow could be due to an increase in the NADH/NAD+ ratio, directly by a decrease in Na^+ K^+ ATPase activity.

2. Protein kinase C:

Hyperglycemia also increases the synthesis of diacylglycerol (DAG) by enhancing the metabolism of glucose to diacylglycerol precursors through glycolysis. This cellular metabolic regulator activates an important signal transducer, the protein kinase C (PKC) pathway. Particularly, isoform is more activated in the heart and the aorta of diabetic rats. Hyperglycemia increases diacylglycerol production and protein kinase C activation, leading to a decrease in eNOS and an increase in the production of prostanoid substances by the endothelium. The increased concentrations of endothelin-1 (ET1) in type 2 diabetes mellitus are due to the enhanced ET1 production caused by hyperglycemia, partly via activation of PKC-β and δ isoforms.

The adverse effects of elevated glucose levels on ACh-induced relaxation of rabbit aorta and rat pial arterioles were restored by the addition of protein kinase C-inhibitors. In addition, the glucose-induced release of vasoconstrictor prostanoids was prevented by protein kinase C-inhibition. In experimental diabetes, protein kinase C-inhibitors improved endothelial dysfunction in pial arterioles in vivo, but not in isolated mesenteric arteries.

3. AGEs:

Glucose is known to bind non-enzymatically to free amino groups on proteins or to lipids. Through a series of oxidative and non-oxidative reactions, AGEs are formed irreversibly and accumulate in tissues over time. AGE formation occurs during the normal ageing process, it is markedly accelerated during diabetes, as a consequence of an increase in substrate, e.g. glucose, and in the prevailing oxidant stress in this disease. The pathogenicity of AGEs is related to their ability to accumulate in tissues with the formation of cross-links, and to generate oxygen-derived free radicals. In addition, the interaction of AGEs with their cellular receptors (RAGEs) may trigger sustained cellular activation and a further increase of the oxidative stress. Treatment with aminoguanidine, an inhibitor of AGE formation, has proven beneficial on the progression of a broad range of diabetic complications in animal models and is currently under study in human diabetes. AGEs are known to quench NO.

Oxidative stress: Oxidative stress is defined as an increase in the steady-state levels of reactive oxygen species and may occur as a result of increased free radical generation and/or decreased anti-oxidant defense mechanisms.

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Although there is controversy about the antioxidant status in diabetes, several studies have reported decreased plasma or tissue concentrations of superoxide Dismutase, catalase, glutathione and ascorbic acid in both clinical and experimental diabetes.

1. Increase in oxidable substrates

Glucose oxidation leads also to the production of reactive oxygen species (ROS), such as superoxide (O_2•) *via* the cyclooxygenase pathway, hydrogen peroxide (H_2O_2) and hydroxyl radicals (HO•). Studies on the aorta of streptozotocin-induced diabetic rat showed the hyperproduction of O_2• and H_2O_2, leading to the formation of hydroxyl radicals. The superoxide inhibits NO and decreases the relaxation of smooth muscle cells. In diabetic humans, the production of free radicals decreases NO secretion by endothelial cells, and also inactivates NO in the sub-endothelial space. Reactive oxygen species can also alter lipids and proteins, and accelerate the formation of AGE. NO rapidly reacts with O_2• to form peroxynitrite (ONOO-), which may promote LDL oxidation. HO• is responsible for the attack by radicals on phospholipids rich cell membranes, leading to lipid peroxidation.

2. Decreased antioxidant defences

Hyperglycemia also promotes glycation and inactivation of antioxidant proteins, such as Cu/Zn superoxide dismutase (SOD), leading to its inactivation and a reduction in antioxidant defense. Experimental studies in streptozotocin-induced diabetic rats have shown decreased concentrations of antioxidants like vitamin E, superoxide dismutase and catalase. For example, the consumption of NADPH by the polyol pathway leads to decreased gluthatione activity, which is an efficient system for capturing free radicals. Experimentally *in vitro*, when the activities of superoxide dismutase (which capture O_2•) and catalase (which capture H_2O_2) were maintained, the endothelial function was not altered even in cases of hyperglycemia.[3]

CONCLUSION

Diabetes leads to acute changes in endothelium which resulted in endothelial dysfunction. Endothelial dysfunction is mainly occurred due to imbalance between vasoconstrictor and vasodilator mediators in body. Diabetes resulted into increase in oxidative stress which means increase in the steady-state levels of reactive oxygen species and may occur as a result of increased free radical generation and/or decreased anti-oxidant defense mechanisms. Nitric oxide is potent vasodilator present in our body which is released from endothelium. To prevent its metabolism is most important to treat diabetes or to reverse endothelial dysfunction. At the same time vasoconstrictor mediator are also important.

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