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Perspective

The Development and Progression of Diabetic Complications

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DESCRIPTION

Diabetes and its complications are becoming the world's most vital reason for morbidity and mortality. The adverse effects of persistently elevated plasma glucose levels on the various body parts varies in step with the cell types. The cells expressing high levels of the glucose transporter 1 (GLUT 1), like vascular endothelial cells, are unable to control intracellular glucose concentrations and are additional liable to hyperglycaemia-induced damage. Renal mesangial cells are overexpressing GLUT 1 acquire characteristics of the diabetic phenotype, together with the activation of the polyol pathway and enhanced Extracellular Matrix (ECM) synthesis [1]. One among these events is formation of Advanced Glycation End product (AGEs). The elevated levels of glucose starts forming covalent adduct with plasma proteins through a non-enzymatic method called glycation.

Protein glycation reactions resulting in AGEs are thought to be the most important causes of various diabetic complications. High glucose levels may induce glycation of varied structural and functional proteins together with plasma proteins and collagen [2]. The non-enzymatic modification of plasma proteins like albumen, fibrinogen and globulins could also be produce numerous injurious effects including alteration in drug binding within the plasma, blood platelet activation, generation of element free radicals, impaired fibrinolysis and impairment immune system regulation. On the opposite hand, the structural impairment in collagen alters the osteoblast differentiation resulting in bone remodeling and skeletal fragility [3,4].

Advanced glycation is one among the most important pathways concerned within the development and progression of various diabetic complications including renal disorder, retinopathy and neuropathy. Tissue and circulating AGE levels are higher in smokers with concurrent increase in inflammatory markers. There is the evidence from animal studies that exposure to high levels of exogenous AGEs contributes to nephritic and vascular complications. AGEs typically accumulates intracellular as a result of their generation from glucose-derived dicarbonyl precursors. These intracellular AGEs play important roles as stimuli for activating intracellular signaling pathways. AGEs accumulate in most sites of diabetes complications, together with the kidney, retina, and arteriosclerosis plaques. Glycation of proteins interferes with their functions by disrupting molecular conformation, altering enzymatic activity and reducing degradation capability.

The mechanism by that glycation alters the cell functions include denaturation and functional decline of the target macromolecule, protein and lipid, organopathy due to accumulation of AGEs in tissue, activation of receptor-mediated signal pathway in cells, generation of aerobic stress and carbonyl stress. The intermolecular collagen cross-linking caused by AGEs leads to diminished blood vessel and heart muscle compliance, increased vascular stiffness, increase in diastolic disfunction and systolic hypertension. The presence of autoantibodies against serum AGEs are capable of forming AGE-immune complexes in diabetic patients and will play a task in atherogenesis. Glycation-derived free radicals will cause protein fragmentation and oxidization of nucleic acids and lipids. The amino teams of Adenine and guanine bases in DNA are liable to glycation and AGE formation. This review discusses the glycation of proteins like albumen, fibrinogen, globulins and collagen to form differing types of AGEs. The role of AGEs within the pathological process of diabetic complications together with retinopathy, cataract, neuropathy, renal disorder and myocardiopathy is additionally mentioned [5].

During long standing hyperglycaemic state in diabetes, glucose forms covalent adducts with the plasma proteins through a non-enzymatic method called glycation. Protein glycation and formation of Advanced Glycation End product (AGEs) play a very important role within the pathological process of diabetic complications like retinopathy, renal disorder, neuropathy and cardiomyopathy together with other diseases like autoimmune disorder, pathology and aging. Glycation of proteins interferes with their functions by disrupting molecular conformation, altering catalyst activity, and interfering with receptor functioning. AGEs form intra- and extracellular cross linking not only with proteins, however with another endogenous key molecules together with lipids and nucleic acids to contribute within the development of diabetic complications. Recent studies stated that AGEs interact with plasma membrane

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localized receptors for AGEs (RAGE) to change intra gene expression, release of pro-inflammatory molecules and free radicals cellular signaling, organic phenomenon, unleash of pro-inflammatory molecules and free radicals. This review discusses the glycation of plasma proteins like albumen, fibrinogen, globulins and albuminoid to create differing types of AGEs.

The formation of advanced glycation end product seems to be increased within the diabetes as results of hyperglycaemia. Increased glycation and accumulation of glycated plasma proteins have an important role within the pathologenesis numerous diseases. A group of chemical compounds are generated that activate the intracellular signaling pathways and generation of proinflammatory and prosclerotic cytokines that leads to the development and progression of diabetic complications. There is an important role of RAGE within the pathological process of diabetic complications and molecular mechanism of activation of RAGE has to be investigated. The possibility of reducing glycation and tissue AGEs or by block RAGE is an approachable target of delaying or preventing the onset of diabetic complications. Varied compounds each natural and pharmacological are under investigation for their therapeutic potential.

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