Gavin Publishers
Gavin Journal of Diabetes and Metabolic Disorders
Volume 2016; Pages 4
Raikou VD and Kyriaki D

Review Article

A Perspective on Diabetic Complications

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Citation: Sheriiff DS, Khalid G (2016) A Perspective on Diabetic Complications. Gavin J Diabetes Metab Disord 24-27.

Received Date: 30 July, 2016; **Accepted Date:** 13 August; 2016; **Published Date:** 17 August, 2016

Introduction:

In diabetes, the microvasculature shows both functional and structural abnormalities. The structural hallmark of diabetic microangiopathy is thickening of the capillary basement membrane [1-2]. The main functional abnormalities include increased capillary permeability, blood flow and viscosity, and disturbed platelet function [3]. These changes occur early in the course of diabetes and precede organ failure by many years. Increased capillary permeability is manifested in the retina by leakage of fluorescein [4,5] and in the kidney by increased urinary losses of albumin which predict eventual renal failure [5,6], platelet abnormalities, may cause stasis in the microvasculature, leading to tissue hypoxia.

The production by endothelium cells of von Wille brand factor 10 and endothelial-derived relaxing factor and other substances may also be abnormal in diabetes and could contribute to microthrombus formation [7-11].

Hypotheses Regarding the Potential Role of Non-enzymatic Glycosylation and Browning in the Pathology Associated with Diabetes Mellitus [12]

I. Structural proteins

A. Collagen: Decreased turnover, flexibility, solubility; increased aggregating potential for platelets, binding of immunoglobulins, crosslinking, and immunogenicity.

B. Lens crystallins and membrane: Opacification, increased vulnerability to oxidative stress.

C. Basement membrane: Increased permeability, decreased turnover, increased thickness.

D. Extracellular matrix: Changes in binding to other proteins.

E. Hemoglobin: Change in oxygen binding.

F. Fibrin: Decreased enzymatic degradation.

G. Red cell membrane: Increased rigidity.

H. Tubulin: Cell structure and transport.

I. Myelin: Altered structure and immunologic recognition.

II. Carrier proteins

A. Lipoproteins: Alternate degradative pathways and metabolism by macrophages and endothelial cells, increased immunogenicity.

B. Albumin: Alteration in binding properties for drugs and in handling by the kidney.

C. Immunoglobulin G: Altered binding.

III. Enzyme systems

A. Cu-Zn superoxide dismutase

B. Fibrinogen: Altered coagulation.

C. Antithrombin III: Hypercoagulable state.

D. Purine nucleoside phosphorylase: Aging of erythrocytes.

E. Alcohol dehydrogenase: Substrate metabolism.

F. Ribonuclease A: Loss of activity.

G. N-acetyl-D-glucosaminidase: Loss of activity.

H. Calmodulin: Decreased calcium binding.

IV.Nucleic acids

Age-related changes, congenital malformations.

V. Potentiation of other diseases of postsynthetic protein modification.

A. Carbamylation-associated pathologic changes in uremia.

B. Steroid cataract formation.

C. Acetaldehyde-induced changes in alcoholism.

Biochemical Basis of the Microvascular Complications

Prolonged exposure to elevated glucose concentrations damages tissues by causing either acute, reversible metabolic changes (due to increased polyol pathway activity, decreased myoinositol and altered diacylglyceral levels, or glycosylation of proteins), or due to formation of Advanced Glycosylation End products (AGE) [12,13]. In insulin-independent tissues such as nerve, the renal glomerulus, lens and retina, hyperglycemia causes elevated tissue glucose levels. The enzyme aldose reductase catalyses reduction of glucose to its polyol, sorbitol, which is subsequently converted to fructose [14]. Sorbitol does not cross cell membranes and its accumulation may cause damage to the lens and altered redox state of pyridine nucleotides [15].

Early glycosylation products form on proteins as glucose attaches to amino groups. These Schiff base adducts then undergo 'Amadori' rearrangement to form stable products analogous to glycosylated haemoglobin which may affect the function of a number of proteins and responsible for free radical-mediated damage in diabetes [16,17] (Figure1 and 2).

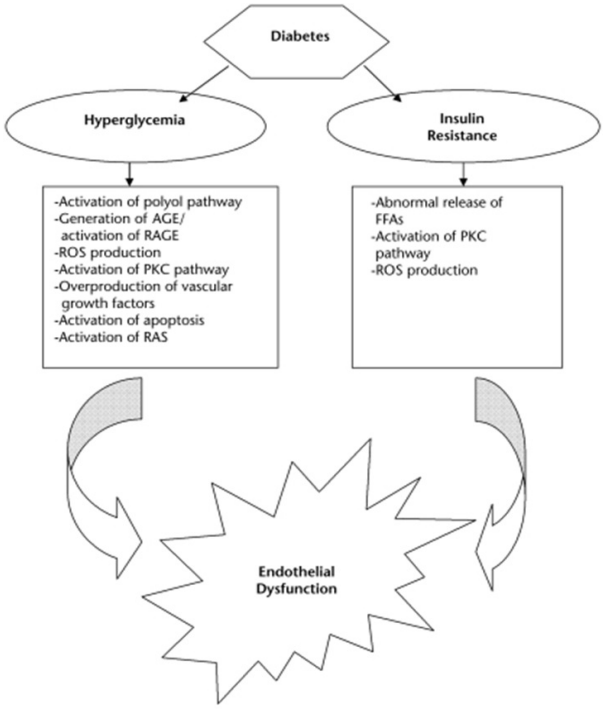

Figure1: Diabetes Mellitus and Hyperglycemia – abnormal glycosylation causing Endothelial Dysfunction.

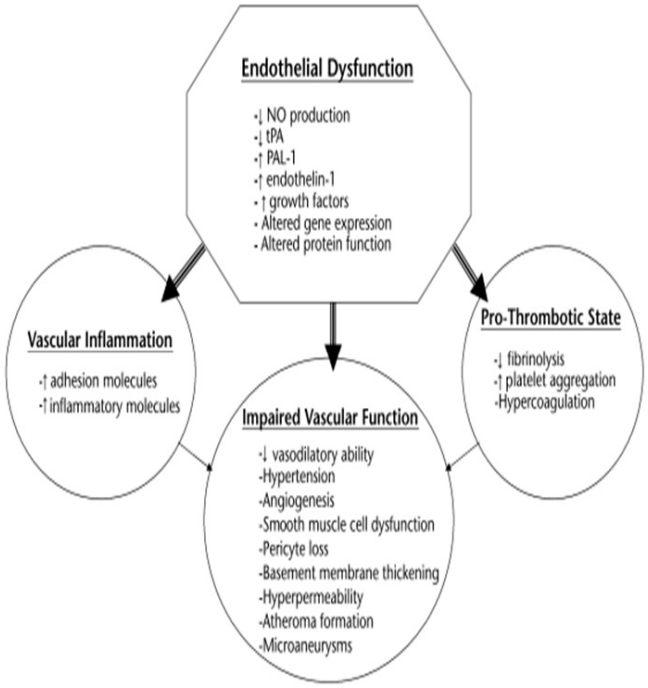

Figure 2: Possible complications following Endothelial Dysfunction Pathological consequences of AGE cross-linking include covalent binding of proteins (e.g. LDL, albumin and IgG) to vessel walls, cross-linking of matrix components in vessel walls causing resistance to enzymatic degradation. Monocyte macrophages have a high-affinity receptor for AGE and binding may release cytokines such as Tumor Necrosis Factor (TNF) and interleukin-1 (IL-1) [18-21]. AGE also form on nucleic acids and histones and may cause mutations and altered gene expression [22,23].

Complications of Diabetes:

Receptors for Advanced Glycation End Products (RAGE) as a probable mechanism for precipitating Diabetic Complications

AGE interaction with cellular receptors (RAGE) plays a vital role in the pathogenesis of diabetic complications. RAGE has three extracellular domains, a V-type ligand binding domain, C1, C2 C-type immunoglobin domains , a transmembrane helix and a short cytosolic tail, fourth transmembrane domain that anchors RAGE onto the membrane that interacts with cytosolic transduction molecules. RAGE's interaction with AGE on macrophages causes oxidative stress and activation of nuclear factor-κB (NF-κB) via activation of the p21ras and the Mitogen-Activated Protein (MAP) kinase signaling pathway. Endothelin-1, tissue factor and thrombomodulin and generation of pro-inflammatory cytokines such as interleukin-1 α (IL-1α), interleukin-6 (IL-6) and Tumour Necrosis Factor-α (TNF-α) production modulated by NF-kB. Adhesion molecules including Vascular Cell Adhesion Molecule-1 (VCAM-1) and InterCellular Adhesion Molecule-1 (ICAM-1) are also expressed more in addition to other effects such as increased vascular permeability. Figure 3. [24,25]

The 'microvascular' (mircoangiopathic or small-vessel) complications of diabetes include retinopathy, nephropathy and neuropathy.

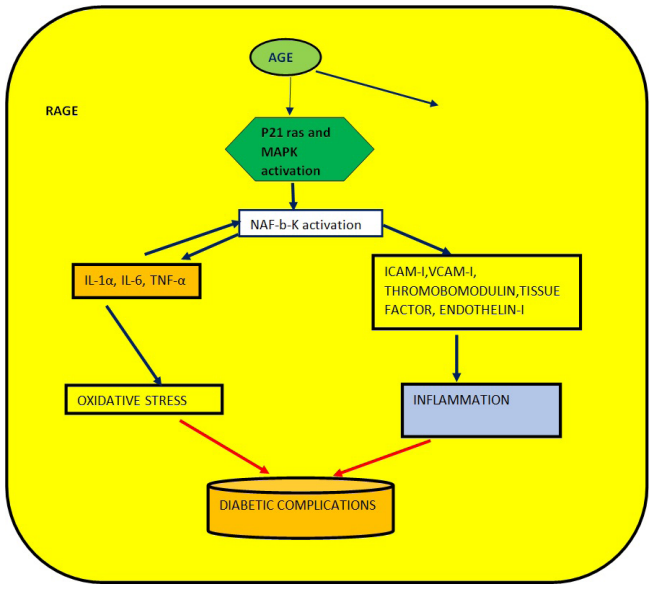

Figure 3: Interaction of AGE with RAGE leading to oxidative stress and initiation of inflammation cascade involving activation of MAPK pathway, NF-kB, IL-6, TNF-α, expression of ICAM-1 and VCAM-2 which ultimately leads to diabetic complications.

Retinopathy:

The earliest lesions of diabetic retinopathy, are thickening of the capillary basement membrane and the capillary dilatation is the first abnormality which may lead to haemorrhages or exudates.

Capillary leakage of plasma lipids and proteins, increased polyol activity generates sorbitol under hyperglycaemic conditions associated with abnormalities myoinositol depletion and reduced Na^{+}-K ATPase activity [26,27]. Neovascularization begins with dissolution of extracellular matrix and proliferation of vascular cells into a solid cord which later canalizes [28]. The incidence of proliferative retinopathy, the principal cause of blindness in IDDM, does not decline even after many years of diabetes suggests that almost all IDDM are susceptible to this complication, just as they are to background lesions [29,30].

Diabetic Nephropathy

Only a subset of patients are susceptible to diabetic nephropathy. Susceptibility to nephropathy has recently been attributed to a genetic predisposition to hypertension, as indicated by parental history of high blood pressure [31]. Diabetic nephropathy is characterized by persistent proteinuria, decreasing glomerular filtrating rate (GFR) and increasing blood pressure [32].

Increased permeability of glomerular capillaries has been suggested as a very early abnormality in patients with diabetes. Microalbuminuria, thought to precede overt diabetic nephropathy before the development of gross proteinuria [33,34].

Diabetic Neuropathy

Diabetic neuropathy can be classified as either reversible or established. The epidemiology of diabetic neuropathy is unclear because of inconsistent definitions of what constitute neuropathy. Chronic sensory neuropathy causes unpleasant sensations, pain in legs and feet, numbness, tingling and muscle wasting due to decreased motor and sensory nerve conduction caused by axonal degeneration and demyelination [35,36]. Peripheral nerve damage contribute to the problems of diabetic foot and male impotence [37] Late autonomic neuropathy manifestations include generalized sweating disorders, postural hypotension, gastrointestinal problems, cardiovascular and genitourinary neuropathy [38,39] One of the mechanisms suggested for diabetic neuropathy is reported to be that interactions between AGEs and RAGE facilitate endo-neural vascular dysfunction, leading to microangiopathy in the peripheral nerve [40].

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