Pathogenesis Aspects of Microvascular Complications in Diabetic Retinopathy: Narrative Literature Review

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1. Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by chronic hyperglycemia resulting from absolute or relative insulin deficiency. Chronic hyperglycemic conditions in diabetes mellitus can cause cellular changes that result in chronic complications, both macrovascular and microvascular. There are two types of diabetes mellitus, namely DM Type 1, or known as insulin-dependent diabetes mellitus (IDDM). This type is caused by damage to pancreatic beta cells that causes total insulin deficiency. The process of type 1 DM occurs due to idiopathic or autoimmune processes. DM type 2 or non-insulin-dependent diabetes mellitus (NIDDM), this type occurs due to impaired insulin secretion or insulin resistance.1-4

Mechanisms of Hyperglycemic Toxicity

Several mechanisms are thought to cause microvascular damage and retinopathy in diabetes. These include the polyl pathway, formation of advanced glycation end products (AGE), activation of protein kinase C (PKC), oxidative stress, and increased activity of the hexosamine pathway.
Polyol/Sorbitol pathway

In DM, there is an excess amount of glucose metabolized by the body. This pathway is controlled by two enzymes. The first enzyme is aldose reductase, which reduces glucose to sorbitol using the cofactor nicotinamide adenine dinucleotide phosphate (NADPH). Then sorbitol is converted to fructose by sorbitol dehydrogenase (SDH). Sorbitol is hydrophilic and cannot diffuse into cell membranes, resulting in accumulation that causes retinal vascular endothelial osmotic dysfunction, pericyte loss, and basement.\textsuperscript{5-7}

![Polyol/Sorbitol pathway diagram](image)

Figure 1. Polyol/Sorbitol pathway.

The product of sorbitol is converted into fructose which then binds to phosphate to form fructose-3-phosphate and is broken down into 3-deoxyglucosone, which is then formed into advanced glycation end products (AGE).

Increased AGE formation

AGES are proteins or fats resulting from non-enzymatic glycation reactions and oxidation after exposure to aldose sugars. The initial product of the non-enzymatic reaction is the Schiff base, which then spontaneously turns into the Amadori product. The glycation of proteins and fats causes molecular changes that produce AGEs. AGE is found in retinal blood vessels with serum levels correlated with the severity of retinopathy. AGE can bind to cell surface receptors such as RAGE, galectin-3, CD36, and macrophage receptors. AGE modifies hormones, cytokines, and extracellular matrix, resulting in vascular damage. In addition, AGE also inhibits DNA synthesis, increases VEGF mRNA, increases NF-kB in vascular endothelium, and triggers retinal pericyte apoptosis.\textsuperscript{8-11}
**Activation of PKC**

Protein Kinase C (PKC) is a serine kinase that plays a role in hormonal, neuronal transduction, and *growth factors*. Hyperglycemia increases levels of diacylglycerol (DAG), which causes an increase in PKC activation.

PKC activation causes various changes in endothelial permeability, hemodynamics, leukostasis, apoptosis, cytokine activation, basement membrane thickening, and abnormal angiogenesis.\(^\text{14}\)

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*Figure 2. Formation of advanced glycation endproducts (AGE).\(^\text{12}\)*

*Figure 3. PKC activation\(^\text{15}\)*
**Oxidative stress**

Oxidative stress is a severe complication that can lead to microvascular complications and is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to eliminate ROS with antioxidants. In normal physiology, ROS helps the body damage foreign microorganisms that can damage cells. However, high ROS levels can damage cells through lipid peroxidation, DNA modification, protein destruction, and mitochondrial damage. Oxidative stress causes various damage to cell components and contributes to the pathogenesis of various diseases.16,17

**Hexosamine pathway**

The hexosamine pathway is activated when there is excess intracellular glucose that cannot be broken down by glycolysis. Normally, excess glucose is converted to glucose-6-phosphate, which is converted to fructose-6-phosphate. In DM, fructose-6-phosphate is converted to N-acetyl-glucosamine-6-phosphate by glutamine fructose-6-phosphate amidotransferase (GFAT). The high production of glucosamine-6-phosphate triggers the production of uridine diphosphate N-acetyl glucosamine (UDP-GlcNAc) which causes changes in protein function and gene expression that reduce cell protection and can induce apoptosis.18-20

2. **Conclusion**

There are several mechanisms thought to cause microvascular damage and retinopathy in diabetes, namely the polyol pathway, formation of advanced glycation end products (AGE), activation of protein kinase C (PKC), oxidative stress, and increased activity of the hexosamine pathway.

3. **References**


