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

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ABSTRACT

Chronic hyperglycemic conditions in diabetes mellitus can cause changes that result in chronic complications, both macrovascular and microvascular. 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.

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 polyol 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. [5-7]

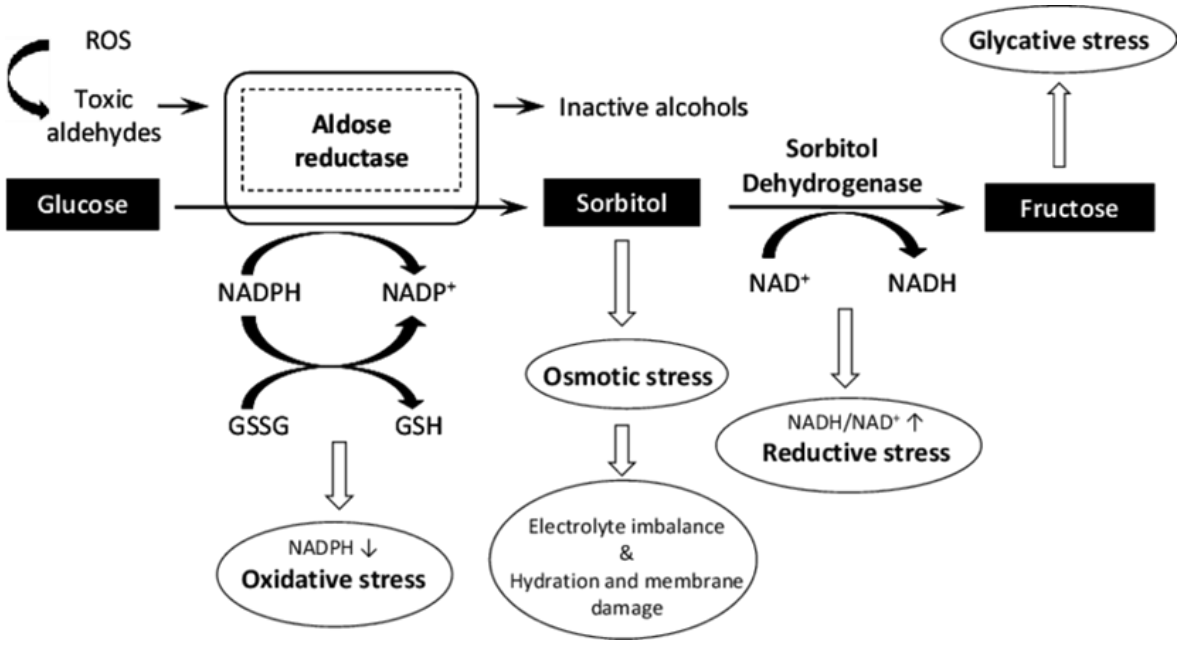

Figure 1. Polyol/Sorbitol pathway.

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.[8-11]

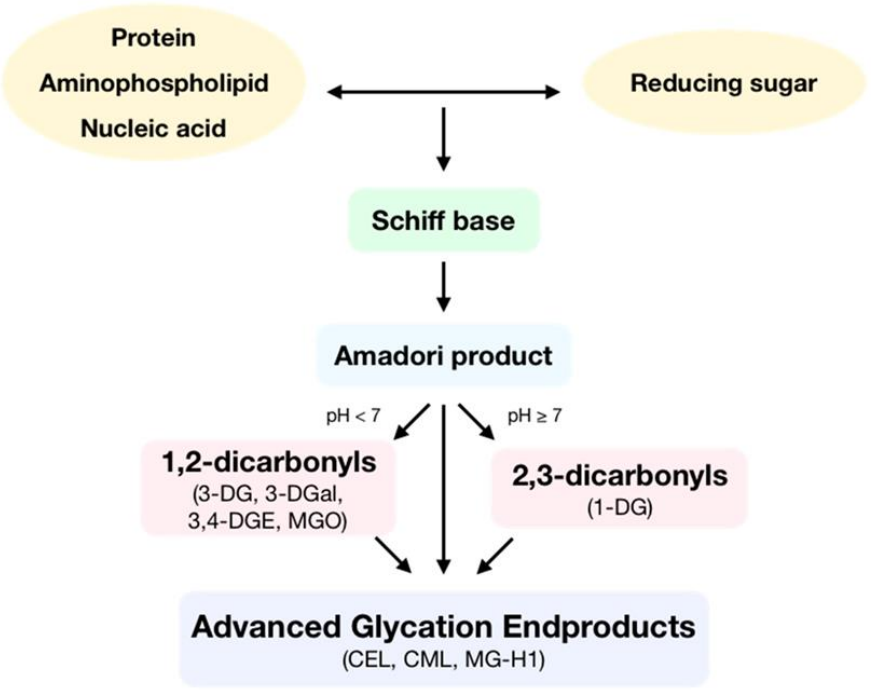

Figure 2. Formation of advanced glycation endproducts (AGE).[12]

Activation of PKC

Protein Kinase C (PKC) is a serine kinase that plays a role in hormonal, neuronal transduction, and *growth factor*s. 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.[14]

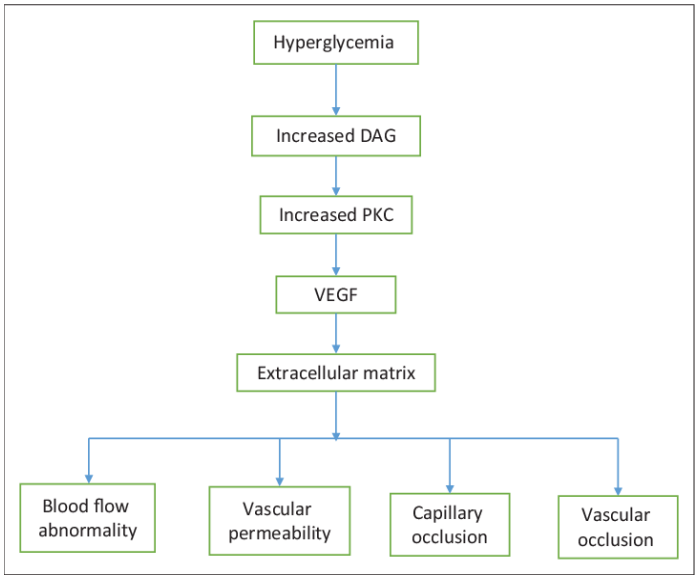

Figure 3. PKC activation[15]

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

1. Glovaci D, Fan W, Wong ND. Epidemiology of Diabetes Mellitus and Cardiovascular Disease. Curr Cardiol Rep. 2019 Mar 4; 21(4): 21. doi:10.1007/s11886-019-1107-y. PMID: 30828746.
2. Endris T, Worede A, Asmelash D. Prevalence of Diabetes Mellitus, Prediabetes and Its Associated Factors in Dessie Town, Northeast Ethiopia: A Community-Based Study. Diabetes Metab Syndr Obes. 2019; 12: 2799-2809. Doi: org/10.2147/DMSO.S225854.
3. Cheloni R, Gandolfi SA, Signorelli C, et al. Global prevalence of diabetic retinopathy: protocol for a systematic review and meta-analysis. BMJ Open 2019; 9: e022188. doi:10.1136/ bmjopen-2018-022188.
4. Ang Xiao, Hui Feng Zhong, Lei Xiong, Lin Yang, et al. Sequential and Dynamic variations of IL-6, CD18, ICAM, TNF-, and Microstructure in the Early Stage of Diabetic Retinopathy. Disease Markers. 2022;22. https://doi.org/10.1155/2022/1946104.
5. Zhang W, Chen S, Liu ML. Pathogenic roles of microvesicles in diabetic retinopathy. Acta Pharmacol Sin. 2018; 39(1): 1–11. Available from: http://dx.doi.org/10.1038/aps.2017.77
6. Liu L, Zuo Z, Lu S, Liu A, Liu X. Naringin attenuates diabetic retinopathy by inhibiting inflammation, oxidative stress, and NF-κB activation in Vivo and in Vitro. Iran J Basic Med Sci. 2017; 20(7): 814–22.
7. Rübsam A, Parikh S, Fort PE. Role of inflammation in diabetic retinopathy. Int J Mol Sci. 2018; 19(4): 1–31.
8. Chandra S, Sheth J, Anantharaman G, Gopalakrishnan M. Ranibizumab-induced retinal reperfusion and regression of neovascularization in diabetic retinopathy: An angiographic illustration. Am J Ophthalmol Case Reports [Internet]. 2018; 9(December 2017): 41–4. Available from: https://doi.org/10.1016/j.ajoc.2018.01.006

9. Song P, Yu J, Chan KY, Theodoratou E, Rudan I. Prevalence, risk factors and burden of diabetic retinopathy in China: a systematic review and meta-analysis. J Global Health. 2018 Jun; 8(1): 01803.
10. Croft M, Siegel RM. Beyond TNF: TNF superfamily cytokines as targets for the treatment of rheumatic diseases. Nat Rev Rheumatol. 2017; 13(4): 217–33.
11. Cen S, Hsu Y, Lin Y, Huang YC, Chen CJ, Lin WD, et al. Current concepts regarding developmental mechanisms in diabetic retinopathy in Taiwan. Biomedicine. 2016; 6: 1-8.
12. Eshaq RS, Aldalati AMZ, Alexander JS, Harris NR. Diabetic retinopathy: Breaking the barrier. Pathophysiology. 2017; 24(4): 229-41.
13. Elia J. Duh, Jennifer K Sun, Alan W. Stitt· Diabetic retinopathy: current understanding, mechanisms, and treatment strategies· JCI Insights. 2017; Jul 20; 2(14). Pii: 93751. Doi: 10.1172/jci.insight.93751.
14. Mathebula SD. Biochemical changes in diabetic retinopathy triggered by hyperglycaemia: A review. Afr Vision Eye Health. 2018; 77(1): a439.
15. Feng Y, Gross S, Chatterjee A, Wang Y, Lin J, Hammes HP. Transcription of the inflammatory cytokine TNFα is upregulated in retinal angiogenesis under hyperoxia. Cell Physiol Biochem. 2016; 39(2): 573–83
16. Yao Y, Li R, Du J, Li X, Zhao L, Long L, et al. Tumor necrosis factor-α and diabetic retinopathy: a review and meta-analysis. Clinica Chimica Acta. 2018; 485: 210–7.
17. Amin R, Ansyori AK, Erna R, Fauzi L. Anti-Receptor Advanced Glycation End Products Decreases Inflammatory Pathways in Diabetic Retinopathy: In vivo Study. Open Access Maced J Med Sci. 2020; 8(A): 414-417. https://doi.org/10.3889/oamjms.2020.4293.
18. Saleh I, Maritska Z, Parisa N, Hidayat R. Inhibition of receptors for advanced glycation end products as new promising strategy treatment in diabetic retinopathy. Open Access Maced J Med Sci. 2019; 7(23): 3921–4.
19. Atli H, Onalan E, Yakar B, Duzenci D, Dönder E. Predictive value of inflammatory and hematological data in diabetic and non-diabetic retinopathy. Eur Rev Med Pharmacol Sci. 2022; 26(1): 76-83. doi: 10.26355/eurrev_202201_27750.
20. Wu G, Liu B, Wu Q, Tang C, Du Z, Fang Y, Hu Y, Yu H. Correlations between different angiogenic and inflammatory factors in the vitreous fluid of eyes with proliferative diabetic retinopathy. Front Med (Lausanne). 2021; 28; 8: 727407. doi: 10.3389/fmed.2021.727407.