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Review Article

Hyperglycemia-induced oxidative stress in the development of diabetic retinopathy

Ahmed Thabit Alnahdi[1]*, Lama Abdulaziz Almujalli[2], Sahar Yousef Alhawsawi[3], Raneem Abdurabu Gomawi[4], Abdullah Hazza Alhobera[5], Khawlah Fares Alshammari[6], Mazin Talal Alshammari[5], Hisham Muhammedeed Almuallim[7], Gehan Khalid Mubaraki[8], Mansour Adel Shourbaji[9]

[1]Department of Ophthalmology, East Jeddah General Hospital, Jeddah, Saudi Arabia
[2]Riyadh First Health Cluster, Ministry of Health, Riyadh, Saudi Arabia
[3]Department of Ophthalmology, Hera General Hospital, Mecca, Saudi Arabia
[4]College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[5]Hail Health Cluster, Ministry of Health, Hail, Saudi Arabia
[6]Department of Family Medicine, Hail Health Cluster, Hail, Saudi Arabia
[7]Department of Emergency Medicine, Ministry of Health, Jeddah, Saudi Arabia
[8]College of Medicine, Alfaisal University, Riyadh, Saudi Arabia
[9]Department of Cardiology, Madinah General Hospital, Medina, Saudi Arabia

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***Correspondence:**
Dr. Ahmed Thabit Alnahdi,
E-mail: dr_thabit@hotmail.de

ABSTRACT

Diabetic retinopathy (DR), the leading cause of preventable blindness, is primarily caused by chronic hyperglycemia-induced oxidative stress. This review examines molecular mechanisms by which hyperglycemia-induced oxidative damage transmits into retinal tissue. We summarize the major pathways: polyol activation, advanced glycation end-products (AGEs), protein kinase C (PKC) dysregulation, and hexosamine pathway. Oxidative stress leads to mitochondrial dysfunction, apoptosis of retinal endothelium and pigment epithelium and activation of cytokines, as well as overexpression of vascular endothelial growth factor (VEGF). These processes together cause vascular leakage, macular edema and pathological angiogenesis. Trials of oxidative stress therapies (e.g. antioxidants, PKC inhibitors e.g., ruboxistaurin, and anti-VEGF agents e.g., ranibizumab, bevacizumab, aflibercept) as well as mitochondria targeted therapies are considered potential therapeutic approaches to improve DR prognosis. Further studies on DR pathophysiology and treatment are recommended to develop effective interventions for this vision threatening condition. Better prevention and management of DR requires early intervention and biomarker-based approaches.

Keywords: Diabetic retinopathy, Hyperglycemia, Oxidative stress, Inflammation, Mitochondrial dysfunction

INTRODUCTION

Diabetic retinopathy (DR) is one of the most serious microvascular complications of diabetes mellitus, accounting for a significant proportion of preventable blindness worldwide.[1] Based on an epidemiological study conducted in USA, DR manifests in roughly 28.5% of patients with diabetes over age 40 years during the years 2005-2008.[2] DR incidence is predicted to increase significantly, and the number of patients with DR could reach 191 million in 2030.[3]

The pathophysiology of DR is mainly related to chronic hyperglycemia, which initiates a cascade of biochemical

and molecular changes in the retinal microvasculature. Initially, these changes present as non-proliferative DR (NPDR), characterized by the appearance of microaneurysms and mild dilation of retinal blood vessels. Then, proliferative DR (PDR) occurs as DR progresses. PDR is characterized by the development of new blood vessels on the retinal surface. Inevitably, these newly formed vessels are fragile and poorly formed, prone to leakage leading to vitreous hemorrhage or retinal detachment resulting in vision loss.[4,5] Oxidative stress has been identified as a key mediator of oxidant-induced retinal damage, and is among the several pathogenic mechanisms implicated in DR development.[6]

The retina is particularly vulnerable to oxidative damage due to its unique physiological and anatomical characteristics. Retinal tissue is particularly prone to oxidative stress, due to high oxygen consumption, abundance of polyunsaturated fatty acids in membranes of photoreceptor cells and exposure to light. The main polyunsaturated fatty acids in retinal photoreceptor segments are docosahexaenoic acid, arachidonic acid and oleic acid that are present in the retinal photoreceptor segments contributing about 50%, 8% and 10% of total fatty acids respectively. Although these fatty acids are important to retinal function, they are highly susceptible to oxidative damage because of their unsaturated nature.[7,8]

Multiple pathways account for retinal cell dysregulation of the balance between free radical production and antioxidant defence mechanisms during episodes of hyperglycemia. Under high glucose conditions, mitochondrial electron transport chain reaction is dysregulated and, as a result, excessive reactive oxygen species (ROS) are produced.[6,9] The damaging consequences of oxidative stress extend to various cellular components and processes, driving the progression of DR. Oxidative stress inflicts damage upon lipids, proteins, and DNA, disrupting cellular integrity and function.[10] It triggers apoptosis of retinal ganglion cells, pericytes, and endothelial cells, resulting in the vascular abnormalities characteristic of DR.

Oxidative stress also increases retinal inflammation, leading to more tissue damage and worsening of DR. Furthermore, the blood-retinal barrier is disrupted by oxidative stress, thereby causing increased vascular permeability and macular edema.[11]

Recent advances in understanding the molecular mechanisms underlying hyperglycemia-induced oxidative stress have revealed multiple interconnected pathways that contribute to DR pathogenesis. These include the polyol activation pathway, AGEs production, PKC pathway, and the hexosamine pathway.[12] These pathways together with epigenetic modifications creates a vicious cycle of oxidative damage that can persist even after blood glucose return to normal levels. This phenomenon is known as "metabolic memory".[13,14]

Despite significant advances in our understanding of DR pathogenesis, current therapeutic approaches remain limited in their ability to prevent or reverse retinal damage. So, the primary aim of this review is to critically analyze existing evidence concerning the contribution of oxidative stress to DR pathogenensis, highlighting the molecular mechanisms involved, their associations and relevance for therapeutic strategy. The secondary objective is to discuss possible therapeutic interventions aimed at impairing oxidative stress pathways as an approach to slow the progression of this vision threatening disease.

LITERATURE SEARCH

This narrative review is based on a comprehensive literature search conducted on 16 December 2024 using the Medline and Cochrane databases. Medical subject headings (MeSH) and relevant keywords were employed to identify studies discussing hyperglycemia-induced oxidative stress in DR, including molecular mechanisms, cellular pathways, and associated pathophysiological processes. To enhance the search scope, a manual search was performed through Google Scholar, and reference lists of identified articles were examined for additional relevant studies.

The inclusion criteria encompassed articles across all publication dates, languages, and study types to ensure a broad exploration of the available literature on oxidative stress mechanisms in DR. The search specifically targeted research investigating the intricate molecular interactions between hyperglycemia and oxidative stress, cellular responses to oxidative damage in retinal tissues, mechanisms of retinal cell dysfunction, and the pathogenic pathways linking hyperglycemia to retinal complications.

Studies were selected based on their scientific rigor, relevance to the research question, and ability to provide insights into the complex relationship between hyperglycemia-induced oxidative stress and DR development. The methodology aimed to provide a robust foundation for a detailed analytical review of oxidative stress mechanisms in diabetic retinal pathology.

DISCUSSION

Oxidative stress represents a pathophysiological state characterized by an imbalance between the generation and neutralization of free radicals within cellular systems. Molecular species having an unpaired electron in their outer electron shell are known as free radicals and are very reactive in biological systems. These reactive species arise predominantly from dysregulated reactions in mitochondrial electron transport chain, cellular metabolic processes and environmental exposures such as radiation, atmospheric pollutants and industrial chemicals. Significantly toxic ROS include superoxide, hydroxyl and hydrogen peroxide radicals. Free radical production

exceeding the capacity of the cellular antioxidant systems (superoxide dismutases, glutathione peroxidase), and non-enzymatic components (vitamin A, C, E, and glutathione) result in the development of oxidative stress.[15]

Glucose metabolism primarily proceeds through glycolysis and the citric acid cycle, generating reduced forms of nicotinamide adenine dinucleotide (NAD^+) and flavin adenine dinucleotide (FADH) as metabolic intermediates. Reduced species act as electron donors in the mitochondrial electron transport chain, driving ATP production and converting oxygen to superoxide radicals. However, this process remains tightly controlled under physiological conditions, with little ROS being produced and quickly neutralized by cellular antioxidant systems. During the hyperglycemic state characteristic of diabetes mellitus, increased metabolism of glucose produces more than normal amounts of NADH and $FADH_2$ and, as a result, increases electron flux through the respiratory chain. This forms a high electrochemical gradient across the mitochondrial membrane. Once the gradient surpasses a critical threshold, electron transfer at complex III slows, leading to electron buildup at coenzyme Q. These excess electrons reduce molecular oxygen, forming superoxide radicals and disrupting redox balance.[16]

The relationship between obesity and type 2 diabetes mellitus involves complex inflammatory mechanisms. Dysfunctional adipose tissue initiates infiltration by macrophages through signaling of chemoattractant protein-1 (MCP-1), leading a pro-inflammatory cascade. Inflammatory mediators secreted by activated macrophages such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-1β, stimulate expression of nitric oxide synthase. Nitric oxide production is thus elevated, and reacts with mitochondrial derived superoxide to form peroxynitrite, a highly reactive nitrogen species. The insulin signaling pathways are modulated by this molecule, inducing posttranslational protein modifications, in particular tyrosine nitration.[17]

A parallel inflammatory pathway operates in hepatic tissue, where macrophage recruitment activates nuclear factor-κB (NF-κB) and c-Jun amino-terminal kinase-stress-activated protein kinase (JNK-SAPK) signaling cascades. Hepatic steatosis, oxidative stress, and cellular apoptosis are precipitated by this activation. Insulin sensitivity is further compromised by the resulting hepatic dysfunction both directly and indirectly.[18]

PKC-theta knockout models revealed additional molecular pathways that also contribute to systemic insulin resistance, including PKC theta activation and JNK/SAPK signaling in skeletal muscle. The consequence of this complex pathogenic mechanism is a self-maintaining cycle of obesity-induced inflammation and hyperglycemia-mediated oxidative stress that mutually promote metabolic dysfunction to establish a persistent state of oxidative damage at the cellular level.[19]

DR manifests as a progressive microvascular complication characterized by irreversible retinal capillary damage. According to clinical evidence, DR development is directly related to diabetes duration. Based on an epidemiological study, the incidence rate of retinopathy is 17% at 5 years post-diagnosis, with a dramatic increase to 97.5% after 15 years of diabetes mellitus.[20]

The pathophysiological progression of DR involves multiple structural and functional alterations in retinal microvasculature. Basement membrane thickening, increased vascular permeability, tissue ischemia, and increased expression of angiogenic factors occur due to hyperglycemia. In advanced disease stages, pathological angiogenesis develops due to tissue hypoxia and elevated VEGF levels. These newly formed vessels, developing along the posterior vitreous surface, are fragile and leaky, leading to vitreous hemorrhage. Vitreous contraction, developing secondary to disease progression, frequently leads to retinal detachment with resultant severe visual impairment.[21,22]

DR is classified into two distinct clinical phenotypes: non-proliferative and proliferative DR. Early disease stages are represented by NPDR and are characterized by microaneurysm formation, venous beading, and exudate deposition. PDR resulting from disease progression is characterized by pathological neovascularization and its related complications. A study conducted in Cameroon on 407 diabetic patients (49 with type I, 358 with type II) reported that 164 individuals had retinopathy; 104 cases with NPDR and 60 cases with PDR.[23] These data indicate that DR has a significant burden, and its early detection and treatment are important.

Hyperglycemia-induced oxidative stress activates multiple biochemical pathways that play vital roles in DR development. These multifaceted molecular mechanisms lead to significant changes in the structure and functions of retinal cells. A detailed analysis of these pathways and their relations to progression of DR is discussed in the sections below.

Polyol pathway activation and oxidative stress

The polyol pathway, a glucose-metabolic route, represents one of the primary mechanisms through which hyperglycemia induces oxidative stress in retinal tissue. The production of sorbitol, a harmful intermediate, by this pathway contributes to progression of DR. Polyol pathway is activated by hyperglycemia through two enzymes: aldose reductase and sorbitol dehydrogenase. The first enzyme converts glucose into sorbitol by aldose reductase using NADPH as a cofactor. Then, sorbitol is further converted, by sorbitol dehydrogenase, into fructose using NAD^+. However, accumulation of sorbitol occurs inside cells due to its limited permeability across cellular membranes leading to osmotic stress and subsequent cellular damage. Cell death and advancement

of DR occurs due to sorbitol accumulation, combined with unclear mechanisms, leads to cell death and the progression of DR.[24,25]

Hyperglycemia induced mitochondrial oxidative stress exacerbates polyol pathway activity. Through this pathway, excessive superoxide radicals generated in oxidative stress increase flux. The consumption of NADPH, required for regenerating glutathione, a central antioxidant, leads to its deficiency. This results in a decrease of antioxidant defences, and as a result, increased oxidative damage. In addition, formation of reduced glutathione increases aldose reductase activity and downregulates genes in glutathione regulation that can generate more oxidative stress. These interconnected processes constitute a feedback loop in which oxidative stress induces polyol pathway activation – an event which, in turn, increases oxidative damage. Retinal cell injury and DR progression are significantly related to this continuous cycle of stress and damage.[26]

Hexosamine activation pathway

The hexosamine pathway begins with the phosphorylation of glucose to fructose-6-phosphate. The latter is converted to glucosamine-6-phosphate via fructose-6-phosphate amidotransferase (GFAT) using an amino group from glutamine. Glucosamine-6-phosphate undergoes acetylation and isomerization to N-acetylglucosamine-6-phosphate, then UDP-N-acetylglucosamine (UDP-GlcNAc) is eventually generated. Proteoglycans, glycolipids, and glycoproteins are all derived from UDP-GlcNAc. Alternatively, direct phosphorylation of glucosamine by hexokinase leads to formation of glucosamine-6-phosphate, that increases production of UDP-GlcNAc for post-transcriptional modifications.[27]

The hexosamine pathway is implicated in the toxic effects of reactive oxygen species (ROS) during hyperglycemia. Excessive ROS production due to hyperglycemia inhibits glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity. This leads to diversion of glycolytic intermediates into the hexosamine pathway, so glucosamine levels become higher. Hydrogen peroxide (H_2O_2) production is stimulated by glucosamine, resulting in oxidative stress, endothelial damage, increased vascular permeability, and angiogenesis. In addition, GAPDH inhibition activates the advanced glycation end-product (AGE) pathway catalyzed by interaction with methylglyoxal, another source of retinal oxidation and a contributor to vascular complications.

AGEs and oxidative damage

AGEs have an important contribution to DR progression. AGEs are formed in normal people but in diabetic patients the accumulation is accelerated due to excess amount of glucose available. Fructose generated via the polyol pathway is the major AGE precursor and is oxidized at much higher kinetics than glucose. The evidence that fructose 3 phosphate is present in diabetic rat lenses is proof that AGEs are involved in DR pathophysiology.[28,29] Studies show that blocking fructose formation and inhibiting AGE formation tend to slow the progression of the disease.[30]

Binding of AGEs to their receptors (RAGEs), induces damaging effects that are further augmented by oxidative stress. During hyperglycemia, fructose and its metabolites are oxidised by ROS, leading to increased generation of methylglyoxal. Specific AGEs, formed by this highly reactive compound, bind to RAGEs leading to retinal cell inflammation.[31]

The relationship between oxidative stress and AGEs creates a harmful cycle: oxidative stress increases both AGE formation and RAGE expression, while the resulting cellular damage stimulates DR progression. Various molecular pathways, including NF-kB activation and increased binding of transcription factors to RAGE promoters, mediate this cycle.[32]

PKC pathway dysregulation

PKC is a key enzyme that conducts reversible phosphorylation reactions and participates in lipid-related signal transduction. It contains a regulatory N-terminal region and a catalytic C-terminal region. PKC is activated by increased levels of diacylglycerol (DAG) or calcium ions. This normally occurs through a particular pathway involving G-protein coupled receptors. However, this process becomes disrupted during oxidative stress induced by hyperglycemia. Excessively produced ROS interfere with glycolysis, leading to an accumulation of compounds that overstimulate PKC.[33]

This overstimulation causes dysregulation of multiple critical processes at the cellular level, including cellular membrane structure, transcription, immune responses, and cellular growth. Uncontrolled cellular growth is particularly concerning as it triggers angiogenesis, a primary component in DR progression.[34]

This is worsened as PKC affects various growth factors and inflammatory mediators. Expression of VEGF, transforming growth factor-beta 1, plasminogen activator inhibitore1, and NF-kB is increased by specific PKC isoforms.[35-37] This elevated expression leads to several pathological processes: newly formed blood vessels, accumulation of excessive extracellular matrix, disrupted fibrinolysis, and more inflammation. Collectively these mechanisms, caused by PKC overactivation induced by oxidative stress, contribute significantly to the development and progression of DR.[9]

Apoptosis of endothelial cells and oxidative stress

DR is linked closely to apoptosis of retinal vascular cells, mostly caused by hyperglycemia-induced oxidative stress.

Oxidative stress-associated mitochondrial dysfunction is characterized by elevated superoxide radical levels and the release of major apoptotic factors, such as caspases, cytochrome C, apoptosis-inducing factor (AIF), and apoptotic protease-activating factor-1 (APAF-1), into the cytoplasm of retinal endothelial cells. Apoptosis is mediated by these factors through distinct mechanisms.[6]

Caspases are a group of cysteine proteases highly sensitive to oxidative stress and primarily involved in apoptosis. Caspases 2, 8, 9, and 10 are involved in apoptosis initiation, while caspases 3, 6, and 7 execute the process.[38] By inhibition of caspases, apoptosis can be prevented.[39] Mitochondrial swelling and caspase-2 stimulation release cytochrome C from mitochondria, activating caspase-mediated apoptosis.[40] Mitochondria release AIF into the cytoplasm which then enters the nucleus, where it causes DNA fragmentation in coordination with endonuclease G, resulting in endothelial cell death.[41] APAF-1 is essential for apoptosis as it binds cytochrome C to activate caspases. In animal models, APAF-1 deficiency reduced the expression of caspases and blocked apoptotic responses.[42]

Apoptosis induced by oxidative stress of retinal endothelial cells leads to inflammatory responses: activation of cytokine, interleukins and growth factors release. In addition, PKC overactivation increases VEGF expression causing more inflammation. The vascular leakage, vitreous hemorrhages and macular edema characteristic of DR results from this combination of apoptotic and inflammatory changes. Consequently, endothelial cell apoptosis induced by oxidative stress is a critical mechanism to the DR progression.[43]

Destruction of macular pigment

Dietary carotenoids, lutein and zeaxanthin deposited in the retinal pigment epithelium, constitute the macular pigment, which is essential for visual performance and protection against phototoxicity. Carotenoids act as antioxidants, protecting retinal cells from free radical damage induced by ultraviolet radiation, and from age related macular degeneration and diabetic maculopathy.[44]

However, hyperglycemia induced oxidative stress causes apoptosis of the retinal pigment epithelium to disrupt macular pigment through various mitochondrial signaling pathways. Modulation of mitochondrial permeability transition pore increases membrane permeability during mitochondrial dysfunction induced by oxidative stress. As a result, apoptotic mediators, including cytochrome C and the caspases, AIF, and APAF-1 are released, leading to retinal pigment epithelium apoptosis as in retinal endothelial cells.[43]

Protection of retinal lipid membranes from free radical damage, mediated by the macular pigemts, is compromised by retinal pigment epithelium apoptosis. This occurs through compromising the antioxidant defenses of the lutein and zeaxanthin. In turn, oxidative stress is accelerated, retinal cellular structures are damaged, and diabetic macular edema (DME) develops due to vascular leakage. With disease progression, the protective role of macular pigment against concomitant oxidative stress is lost resulting in diabetic maculopathy.[45]

Oxidative stress and inflammation

Inflammation is initiated by oxidative stress by generating free radicals that damage lipid membranes, organelles, and structural proteins, leading to release of cytokines. Interleukins such as IL 1, IL 6, IL 8, and TNF alpha, activated by cytokines intensify inflammation and stimulate vitreous fluid production which results in edema in DR.[46]

Neutrophils are recruited by cytokines to inflammation site, causing tissue damage through endothelial cell injury via activation of macrophages and increased permeability of retinal capillaries. This results in extracellular matrix accumulation and edema surrounding the retina.[47]

NF-kB, activated by oxidative stress, stimulates the release of inflammatory mediators like nitric oxide and prostaglandins. Nitric oxide is a vasodilator that increases fluid accumulation in the retina, while prostaglandin E2 is elevated during PDR, worsening it in conjunction with cytokines and VEGF.[48] IL-1 also increases production of cyclooxygenase-2 (COX-2) that catalyses prostaglandin E2 generation. COX-2 activation alters the expression of VEGF and nitric oxide, where VEGF promotes angiogenesis and nitric oxide induces vasodilation. Both significantly contribute to retinal fluid retention and the progression of DR.[49]

Therapeutic implications and future directions

Current evidence suggests that targeting oxidative stress pathways represents a promising approach for treating DR. Multiple therapeutic strategies have emerged from our understanding of these pathways as follows:

Antioxidant interventions

Recent studies have demonstrated that antioxidant therapy has potential benefits in DR management. Research suggested that antioxidant supplements could diminish hyperglycemia induced retinal oxidative stress, PKC activity, and nitric oxide levels. Microvascular lesions appearing early in NPDR could be ameliorated by Vitamins C and E, along with other antioxidants, However, controlled clinical trials are still required to assess the long-term efficacy of antioxidant therapy.[50]

PKC pathway inhibition

Experimental studies have shown that specific PKC inhibitors development may be promising. Selective PKC-β1 and β2 inhibitor ruboxistaurin (LY333531)

isolated from diabetic animal models prevention of microvascular complications, and ischemia related neovascularization..[51,52]

Anti-VEGF therapy

Based on the understanding of oxidative stress-induced VEGF expression, the anti-VEGF agents have been developed as a therapeutic strategy and used to replace focal macular laser therapy as first line approach. Currently, ranibizumab, bevacizumab, aflibercept are the most widely used anti-VEGF agents.

The restore study demonstrated that ranibizumab, either alone or combined with laser therapy, provided better visual acuity improvements compared to laser treatment alone. Deferred laser with adjunct ranibizumab were found more effective than prompt laser. Ranibizumab treated about 50% of eyes treated with no additional therapy required over five years, suggesting a reduced injection frequency over time.[53]

Another clinical trial further confirmed that early and consistent ranibizumab treatment significantly lowered the risk of developing PDR and prevented retinal nonperfusion over a 5-year period.[54]

Mitochondrial-targeted approaches

Due to the central role of mitochondrial dysfunction in DR pathogenesis, approaches to treat mitochondria dysfunction have been considered. The use of both mitochondrial antioxidant and uncoupling protein modulators to prevent oxidative damage have been studied. Research suggest that protection of mitochondrial DNA and maintenance of the efficiency of electrons transport chain can prevent the development and progression of DR.[55]

CONCLUSION

DR develops through a damage cascade induced by chronic hyperglycemia and oxidative stress. Both lead to disruptions of polyol, advanced glycation end-products, PKC, and hexosamine pathways. These changes lead to mitochondrial dysfunction, excess ROS production, inflammation, cell and vascular apoptosis and abnormal angiogenesis. Interference with these pathways with treatments like antioxidants, PKC inhibitors including ruboxistaurin and anti-VEGF agents including ranibizumab could improve DR outcome. There are promising emerging therapeutic options against mitochondrial dysfunction, though metabolic memory may limit their efficacy. Better prevention and management of DR requires early intervention and biomarker-based approaches.

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