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Review

The Role of Oxidative Stress in the Pathogenesis of Eye Diseases

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ABSTRACT

This article aims to determine the role of oxidative stress (OS) in important eye diseases and draw attention to its importance in eye health. Oxidative stress is an important pathomechanism in many ocular degenerative diseases. This article offers an overview and recent updates on research regarding the mechanism and treatment of eye diseases caused by an imbalance between oxidants and antioxidants. We examine oxidative damage, such as lipid peroxidation, DNA damage, and apoptosis, that occurs in various parts of the eye, including the cornea, anterior chamber, lens, retina, and optic nerve. In particular, we evaluate the association of dry eye, pterygium, keratoconus, glaucoma, cataract, age-related macular degeneration, and diabetic retinopathy with OS. We believe that it will increase clinician awareness as it is a guiding review of natural antioxidant treatments for ocular diseases associated with oxidative stress.

Keywords: Eye disease, eye health, oxidative stress

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INTRODUCTION

Oxidative stress (OS), a condition characterized by an imbalance between the production of reactive oxygen species (ROS) and the capacity of the body's antioxidant defense systems, has emerged as a central mechanism in the pathophysiology of many systemic and ocular diseases [1-5]. In the eye, a highly metabolically active organ with unique exposure to environmental oxidative challenges such as ultraviolet (UV) radiation and high oxygen tension, OS plays a critical role in initiating and propagating pathological processes [6]. This section aims to explain the fundamental relationship between OS and eye diseases, with particular attention to the molecular mechanisms, affected structures, and clinical implications.

The retina, lens, cornea, and other ocular tissues are constantly exposed to ROS generated from both endogenous metabolic activities and exogenous environmental factors [7]. Under physiological conditions, antioxidant systems—including enzymatic antioxidants such as superoxide dismutase (SOD), catalase, and glutathione peroxidase—work in concert with non-enzymatic antioxidants like vitamins C and E to neutralize ROS. However, when OS overwhelms these defenses, it leads to molecular damage, particularly in lipids, proteins, and DNA [4]. Such damage not only disrupts cellular integrity but also induces inflammatory and apoptotic pathways, contributing to tissue dysfunction and disease progression.

Age-related macular degeneration (AMD) and cataracts are two of the most well-studied OS-mediated ocular diseases [8]. In AMD, oxidative damage to retinal pigment epithelial (RPE) cells and photoreceptors is compounded by the accumulation of lipofuscin and drusen, which further perpetuate inflammation and oxidative injury [9]. Similarly, cataractogenesis involves oxidative modifications of lens crystallins, leading to protein aggregation, loss of lens transparency, and visual impairment. Studies suggest that cumulative chronic OS plays a key role in the prevalence of these conditions among aging populations.

Beyond AMD and cataracts, OS has been implicated in the pathogenesis of other eye diseases such as glaucoma, diabetic retinopathy (DR), and keratoconus [10-12]. In glaucoma, elevated intraocular pressure (IOP) induces oxidative stress in the trabecular meshwork, impairing aqueous humor outflow and exacerbating optic nerve damage. In DR, chronic hyperglycemia triggers OS and inflammation, damaging retinal microvasculature and leading to vision-threatening complications. Keratoconus, a degenerative corneal disorder, is associated with oxidative damage to keratocytes and extracellular matrix proteins, contributing to corneal thinning and biomechanical instability.

The recognition of OS as a key driver of eye disease has spurred significant research into antioxidant-based interventions. Dietary and pharmacological antioxidants, such as those used in the Age-Related Eye Disease Studies (AREDS), have demonstrated efficacy in slowing the progression of AMD. Furthermore, novel strategies, including the development of mitochondria-targeted antioxidants and gene therapies aimed at enhancing endogenous antioxidant defenses, hold promise for mitigating oxidative damage in various ocular conditions. However, the clinical translation of these therapies faces challenges, including variability in patient responses and the need for precise delivery systems.

Understanding the role of OS in eye diseases has opened new avenues for both fundamental research and clinical innovation. By targeting oxidative mechanisms, researchers and clinicians aim to preserve vision and improve quality of life for patients affected by these debilitating conditions. The ongoing exploration of OS-related pathways will undoubtedly enhance our ability to diagnose, prevent, and treat eye diseases in the future. In this review, we aimed to provide a better understanding of the mechanism and treatment of OS-related important ocular diseases. In addition, this article draws attention to the therapeutic potential of natural antioxidants in oxidative stress-related eye diseases.

METHODOLOGY

Our review article used literature-inclusive databases such as PubMed and Google Scholar, and studies on oxidative stress-related eye diseases conducted between 2015-2023 were evaluated.

Dry Eye

Dry eye disease (DED) is a multifactorial condition defined by disturbances in the tear film due to reduced tear production or excessive evaporation [13]. As one of the most prevalent ocular surface diseases, DED involves oxidative damage alongside inflammation. It can arise from systemic inflammatory conditions, localized ocular issues, or the use of common medications [14]. Additionally, environmental factors like pollutants, UV radiation, and ozone contribute to increased OS, inflammation, and tear film osmolarity, further impacting the ocular surface [15].

Hyperosmolarity is a key driver in DED pathology, perpetuating oxidative stress-induced damage to ocular epithelial cells. This stress leads to mitochondrial DNA (mtDNA) damage and lipid peroxidation in cell membranes [16]. Furthermore, OS activates inflammatory cascades that release mediators serving as biomarkers in tears [17]. For example, interleukin-6 in tears and conjunctiva stimulates the production of ROS, prostaglandins, and enzymes under conditions of low antioxidant presence [18].

Tear film components, such as lysozymes, immunoglobulins, and antioxidants like lactoferrin, uric acid, and cysteine, are essential for combating oxidative damage. However, tear dysfunction resulting from elevated OS and inflammation can harm glandular and epithelial cells [16]. Animal studies have shown that reduced antioxidant levels in tears promote glandular fibrosis and infiltration of monocytes and neutrophils into the lacrimal glands, leading to severe forms of DED [19]. Nakamura and colleagues demonstrated the accumulation of OS and its correlation with corneal epithelial alterations in a dry-eye mouse model [17]. Evidence highlights the role of OS as a direct and indirect contributor to ocular surface health deterioration, particularly in DED. Aging and numerous acute or chronic conditions exacerbate ROS expression on the ocular surface.

Pterygium

Pterygium is a degenerative condition characterized by fibrovascular tissue growth over the cornea, disrupting tear film stability and causing dry eye. Research has identified oxidative stress as a critical factor in pterygium pathology [20]. Prolonged UV exposure is the primary environmental trigger, resulting in chronic ROS generation and DNA damage [21, 22]. Biomarkers such as increased nitric oxide (NO),

altered antioxidant enzyme levels, modified p53 protein, and elevated 8-hydroxydeoxyguanosine indicate oxidative DNA damage in pterygium tissue [14, 21]. OS promotes inflammation, epidermal hyperplasia, angiogenesis, and lymphangiogenesis within pterygium tissue [22]. Additionally, overexpression of heat shock protein 90 enhances vascular endothelial growth factor (VEGF) activity, driving pterygium-related angiogenesis.

Keratoconus

Keratoconus (KC) is a progressive degenerative disorder marked by corneal thinning and ectasia [23]. It is associated with an imbalance between pro-inflammatory factors and anti-inflammatory defenses [24]. Elevated OS index values have been observed in KC patients, with ROS playing a significant role in its pathogenesis [25]. OS disrupts extracellular matrix components such as collagen types XVIII and XV, leading to ECM remodeling and degradation [19]. Enzymatic activity, particularly matrix metalloproteinases (MMPs) like MMP-2 and MMP-13, is implicated in this process [16, 26]. Additionally, abnormal antioxidant enzyme expression, mitochondrial damage, and stromal thinning contribute to KC progression [27, 28].

Glaucoma

Glaucoma, an age-related disease affecting over 50 million individuals, is the second leading cause of irreversible blindness worldwide. Emerging evidence links glaucoma to oxidative stress, with altered antioxidant defenses and oxidative damage observed in patient tissues [29, 30]. The trabecular meshwork (TM), a critical structure for aqueous humor outflow, is particularly vulnerable to OS due to limited antioxidant capacity [31]. OS damages TM cells, impairing their function and contributing to increased IOP in primary open-angle glaucoma [31]. Studies suggest that mitochondrial dysfunction and chronic ROS production play a significant role in TM cell damage and glaucomatous neurodegeneration [32]. Additional types of glaucoma, such as pseudoexfoliation syndrome and neovascular glaucoma, also exhibit oxidative and inflammatory mechanisms contributing to disease progression [33, 34].

While reducing IOP remains the primary treatment strategy, antioxidants such as omega-3 fatty acids, coenzyme Q10, and vitamins have shown promise in mitigating OS-related damage in glaucoma [35].

Cataract

Cataracts, a leading cause of visual impairment globally, are closely linked to oxidative stress. Factors such as UV exposure, smoking, diabetes, corticosteroid use, aging, and alcohol consumption represent essential risk factors that contribute to lens protein oxidation and opacification [36, 37]. The production of ROS and free radicals-induced oxidative stress is considered one of the effective mechanisms of cataract pathology. This disorder is amplified with reduced endogenous antioxidants with age. Consequently, the crystallin, the major protein in the lens, is oxidized. Oxidative damage to lens proteins, lipids, and DNA leads to structural and functional deterioration, resulting in visual impairment [38]. Lipid peroxidation and imbalances in intracellular ion homeostasis further exacerbate cataract formation [39, 40]. Furthermore, oxidative stress is caused by free radicals or oxidant productions, including lipid peroxidation, protein modification, and DNA damage, and results in cellular degeneration and neurodegeneration from damage to macromolecules. Antioxidant deficiencies are thought to play a role in cataract pathogenesis, highlighting the importance of maintaining oxidative balance [16].

Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in individuals over 50. The pathogenesis involves genetic, environmental, and metabolic factors, with OS playing a central role [41]. The retina, particularly photoreceptors and RPE cells, is highly susceptible to OS due to its metabolic activity and exposure to light [42]. Lipofuscin accumulation, mitochondrial dysfunction, and PUFA oxidation contribute to oxidative damage in AMD [43]. Chronic OS also triggers inflammation, promoting angiogenesis and VEGF-mediated vascular changes [44]. Targeting OS and inflammation may provide therapeutic avenues for AMD management.

Diabetic Retinopathy

Diabetic retinopathy (DR) is a microvascular complication of diabetes, affecting approximately one-third of individuals with the condition. It stands as a leading cause of vision loss among middle-aged and elderly populations and is recognized as a progressively neurodegenerative disease [45]. Early in the disease process, endothelial cell loss occurs due to apoptosis, which subsequently leads to an increase in non-functional, occluded capillaries. This results in heightened vascular permeability, thickened capillary membranes, edema, and hemorrhages. Damaged capillaries leak plasma and red blood cells into nearby retinal tissue, causing occlusions and promoting the release of growth factors like VEGF, which triggers abnormal blood vessel formation [46].

Similar to AMD, oxidative stress plays a role in DR; however, in diabetes, elevated oxidant levels and weakened antioxidant defenses exist independently of age, producing distinct adverse effects. Hyperglycemia not only damages endothelial cells but also enhances mitochondrial ROS production.

This process, influenced by metabolic memory, drives the progression of DR [56]. Excess mitochondrial ROS production can harm mitochondrial DNA and proteins, impairing the electron transport chain. This dysfunction perpetuates superoxide production even when blood glucose levels return to normal, contributing to the continued advancement of DR [47].

Beyond mitochondrial impairment and retinal vascular damage, oxidative stress also impacts the diabetic retina neurologically. ROS reduces levels of brain-derived neurotrophic factor, which is essential for neuronal survival, axonal growth, and synaptic function. Consequently, synaptic damage and neurotrophic factor degradation lead to neuronal cell death and vision problems [42]. Additionally, oxidative stress is closely tied to inflammation, as ROS stimulates both inflammatory responses and angiogenesis. Molecular mechanisms, such as the AGEs pathway, elevate cytosolic ROS and activate the NF-κB signaling pathway [48].

This activation upregulates pro-inflammatory proteins and drives the release of inflammatory mediators, including tumor necrosis factor-alpha, interleukins (IL-6 and IL-8), COX-2, ICAM-1, MCP-1, VEGF, and other cytokines. Furthermore, ROS generated by NADPH oxidase enzymes can activate HIF-1 signaling, which contributes to proliferative diabetic retinopathy and angiogenesis [49]. On a molecular level, oxidative stress also plays a role in diabetic microvascular and macrovascular complications by inducing apoptosis, activating stress-related pathways, damaging proteins, DNA, and lipids, and accelerating AGE formation [42].

Natural Antioxidant Therapy

Antioxidant therapy has been extensively studied for a range of eye conditions, including dry eye, cataracts, glaucoma, and AMD [50-53]. The Age-Related Eye Disease Study (AREDS) study, which used antioxidant treatment containing vitamin C, vitamin E, and beta-carotene, showed that antioxidant treatment had a significant effect on cataracts and effectively slowed the progression of AMD [54].

Vitamin C (also known as ascorbic acid; AA) is used topically in ocular surface diseases and treats corneal epithelial defects. In addition, AA is known to prevent lipid peroxidation and cell apoptosis [55]. Meanwhile, vitamin C supplementation can lower the risk of cataracts in individuals with low antioxidant levels or low plasma AA concentrations [56]. However, some research suggests that vitamin C supplementation does not prevent cataracts, slow their progression, or decrease the likelihood of cataract surgery [57]. Although large-scale clinical trials have shown that AA supplementation does not prevent AMD, in vitro cell studies have demonstrated that pre-treating human RPE cells with AA can help them withstand oxidative stress [58]. In glaucoma, there is currently no consistent result regarding the effect of AA treatment on glaucoma [59]. ROS generated by increased IOP plays a significant role in the apoptosis of RGCs. As a result, managing IOP through AA treatment could potentially help slow down the degeneration of RGCs induced by ROS.

Along with antioxidant vitamins, various other natural antioxidant compounds, such as lutein, zeaxanthin, and curcumin, have been utilized to treat eye diseases associated with oxidative stress [60]. Incorporating lutein and zeaxanthin into the diet can significantly boost macular pigment optical density, which may help improve the proinflammatory and proangiogenic characteristics in patients with AMD. Phytochemical nutrients like green tea catechins, anthocyanins, resveratrol, and Ginkgo biloba have been found to reduce ocular oxidative stress. As a result, further clinical trials in this field are needed.

CONCLUSION

This review article describes oxidative stress in some important ophthalmologic diseases. In dry eye disease, hyperosmolarity triggers oxidative stress-induced damage and leads to mtDNA damage and lipid peroxidation in cell membranes; it also releases the inflammatory cascade in tears. Long-term UV exposure is an important OS trigger in pterygium disease; it causes chronic ROS formation and DNA damage. Keratoconus is primarily inflammatory and has a pathophysiology, but it is known that progression occurs with increasing OS. It is known that mitochondrial dysfunction and chronic ROS production play an important role in TM cell damage and glaucomatous neurodegeneration with increasing OS in glaucoma patients. Cataract is an important cause of visual disability, and its high incidence is due to its association with oxidative stress caused by continuous intraocular penetration and the associated photochemical production of free radicals and other oxidants. Increased ROS production in advanced age and diabetes leads to an impaired antioxidant defense system, causing oxidative damage in the lens. Free radicals oxidize subcellular components such as lipids and phospholipids and can cause membrane lipid peroxidation and trigger the onset of retinopathies. As can be seen, oxidative stress plays an active role in the pathophysiology of many diseases in ophthalmology. Natural antioxidant treatments, including vitamin C, vitamin E, and beta-carotene, contribute positively to reducing the prediction and progression of eye diseases. We believe that it will increase clinician awareness, as it is a guiding compilation of natural antioxidant treatments for ocular diseases related to oxidative stress.

DECLARATIONS

Author Contributions: Concept – HE; Design – HE; Supervision – HE; Data collection and/or processing – BAY; Analysis and/or interpretation – HE, BAY; Literature review – BAY; Writing – BAY; Critical Review – HE.

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