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Review Article

Oxidative stress in ocular pathologies: A focus on redox balance

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Abstract

Preserving the delicate balance between the antioxidant defense mechanisms and oxidative stress caused by the accumulation of ROS/RNS is essential for maintaining redox homeostasis, a critical determinant of ocular health. Imbalances in this system result in oxidative stress, a key pathological factor implicated in numerous eye diseases. This review thoroughly looks at the information that is currently available, illuminating the intricate relationship between mitochondrial malfunction and oxidative stress in conditions that impact the anterior and posterior portions of the eye.

Our analysis highlights the pivotal role of redox imbalance in the onset and progression of major eye conditions while emphasizing the therapeutic potential of strategies aimed at restoring redox equilibrium and fostering regenerative responses. These methods might successfully slow down or stop the development of crippling eye conditions. In addition to improving our knowledge of the molecular processes underlying the pathophysiology of ocular diseases, ongoing research in this area makes it easier to identify new antioxidant targets and treatment approaches. These advancements are expected to transform ocular care, introducing targeted treatments that can greatly enhance the standard of living for those who suffer from disorders that endanger their vision.

Keywords: Ocular disorders, Oxidative stress, Redox homeostasis, Diabetic retinopathy, Eye disorders, Cataract

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1. Introduction

The development of progressive eye problems affecting the posterior area is significantly influenced by oxidative stress (OS), which is brought on by an imbalance between ROS and RNS. Age-related macular degeneration (AMD), diabetic retinopathy (DR), cataracts, and glaucoma are among the conditions that can cause irreversible blindness and provide significant threats to vision. These disorders share complex pathophysiological features, including cellular damage, inflammation, and the effects of OS.[1]

Proteins, lipids, and nucleic acids oxidise as a result of reactive oxygen and nitrogen species produced during oxidative stress. Necrosis, apoptosis, and ultimately cell death are brought on by these reactive chemicals, which interfere with cellular functions including autophagy and mitophagy. Designing successful treatment plans requires an understanding of OS's function in ocular disorders. Aging, a major contributing factor in various disease conditions, involves genetic and epigenetic changes that are intensified by exposure to both internal and external ROS.[2] Biological ageing is mostly determined by the body's ability to cope with cellular stress. The human eye is especially vulnerable to the effects of ageing and OS, despite its intricate structure. The cornea & lens are highly vulnerable to oxidative damage from direct UV exposure, while the metabolically active retina is more affected by age-related processes that promote OS and neurodegeneration.[3]

This thorough analysis looks at the pathological illnesses that impact the main eye tissues, emphasising the intricate connection between OS and the underlying causes of these problems. By exploring these mechanisms, we aim to deepen our understanding of the molecular pathways involved and lay the groundwork for innovative therapies to reduce the impact of OS on ocular health.

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1.1. Oxidative Stress and redox balance

Understanding cellular function and general health requires a knowledge of the intricate idea of OS and the critical role antioxidant defence mechanisms play in preserving cellular equilibrium. OS results from the complex interplay between biological molecules and ROS and RNS. These species are vital to cellular metabolism and are spontaneously created throughout a variety of cellular functions, including immunological reactions and breathing. While ROS and RNS are important for physiological functions like redox signaling and regulated immune responses, their excessive accumulation triggers a cascade of reactions that produce free radicals, leading to damage of biomolecules. Among reactive species, the superoxide anion (O2•) is particularly significant, as it plays a key role in generating various free radicals, including hydroxyl radicals, hydrogen peroxide, peroxynitrite anions, and others. The formation of these free radicals is a characteristic feature of OS, which leads to cellular damage. Furthermore, because of the aerobic respiratory activities they support, mitochondria play a significant role in the generation of both ROS and RNS,[4] Reactive species are produced by a variety of external stimuli, including ionising radiation, xenobiotics, illnesses, and lifestyle choices including smoking and drinking.[5,6,7]

To protect themselves against possible harm brought on by the buildup of ROS and RNS, cells use a strong antioxidant system that consists of both catalytic enzymes and non-catalytic small molecules. ROS and RNS are immediately neutralised by exogenous compounds such vitamins C, E, beta-carotene, and plant polyphenols as well as non-catalytic molecules like bilirubin, glutathione, alpha-lipoic acid, melatonin, and uric acid. Glutathione is particularly crucial for maintaining redox balance and is tightly regulated. Superoxide anions (O2•) are changed into hydrogen peroxide (H2O2) by catalytic antioxidants such superoxide dismutases, which regulate redox signalling and support cellular homeostasis. Hydrogen peroxide (H2O2) is further neutralised by catalase, peroxiredoxins, and glutathione peroxidases, which transform it into oxygen and water. In addition to preventing ROS and RNS-induced cellular damage, this coordinated antioxidant defence mechanism helps to remove nitrogen oxide molecules and denitrosylate proteins.[8]

In conclusion, OS results from an imbalance between the generation of ROS/RNS and the cell's capacity to counteract their deleterious consequences. Radical buildup and consequent cellular component damage are caused by this imbalance. The intricate antioxidant defence system works to combat ROS and RNS, avoiding their excessive accumulation and preserving cellular equilibrium in order to sustain cellular health and function. Developing novel and alternative treatment strategies requires an understanding of the molecular disorders underlying OS and the antioxidant defence system.

2. Discussion

2.1. Oxidative stress and common eye disorder's

2.1.1. Oxidative stress and dry eye diseases

The cornea is a vital part of the eye, serving as a transparent, avascular layer with a thickness of approximately 500 µm. It consists of three main layers: the stromal keratocytes, the stratified epithelium, and a thin layer of endothelium. All these layers play a crucial role in the eye's defense system against environmental threats and pathogens. The epithelial cells of the cornea, being highly exposed to UV light and oxygen, require strong antioxidant defenses to maintain eye health and preserve vision.[9]

Ocular dryness, pain, and tear film instability are the hallmarks of dry eye, a complicated disorder. According to recent research, environmental variables including pollution and UV radiation can produce ROS, which may contribute to the development of dry eye. This aligns with the strong correlation between aging and dry eyes, as the accumulation of ROS increases with age. In a blink-suppressed dry eye model, molecular indicators of OS, including 4-HNE, MDA, and 8-hydroxy-2-deoxyguanosine (8-OHdG), have been detected. 4-HNE and hexanoyl-lysine, two biomarkers of OS, are substantially elevated in those with Sjögren's illness and dry eye as compared to healthy controls.[10,11] Disruption of the three layers of the ocular surface can lead to dry eye disease, which may be triggered by various factors such as environmental conditions, autoimmune diseases, or hormonal changes. Furthermore, dry eye illness can also develop as a result of meibomian and lacrimal gland dysfunction.

The majority of previous research on the role of ROS in dry eye illness has been on meibomian and lacrimal gland dysfunction. In a tetracyclic-mev-1 transgenic mouse model, lacrimal gland impairment and decreased tear production have been noted due to mitochondrial complex II failure. In this model, the genetic dysfunction of complex II in the mev-1 mutant leads to the upregulation of prooxidant production by the mitochondria. The crucial function of OS in reducing tear production by harming the lacrimal gland is demonstrated by the mice with the mutation's elevated mRNA expression of inflammatory markers, increased immune cell infiltration, and damage to the acini structure.[12] In addition to inflicting immediate structural harm, OS may interfere with the neural reflex arc that triggers the release of tears. The cornea and conjunctiva are innervated by sensory nerve terminals from the trigeminal ganglia, which also activate neurones that innervate the lacrimal gland acini and send signals to the central nervous system. Prooxidants on the surface of the eye can cause afferent sensory neurones' myelin to degrade, which lowers signal transmission to the lacrimal gland and, ultimately, tear production.

The meibomian glands, which are found in the tarsal plates of both eyelids, contain prooxidant indicators in the

tear film. Longer tear film breakdown times and lower ocular surface disease index scores are correlated with these indicators. A study that excluded a hyaluronic acid-only group casts doubt on the controversial advantages of adding Vitamin B12. Iodide, acting as a reducing agent, efficiently neutralizes oxidants, and iodide iontophoresis has been shown to alleviate dry eye symptoms more effectively than a control group. Recent research has highlighted polyunsaturated fatty acids (PUFAs), especially omega-3 fatty acids like docosahexaenoic acid and eicosapentaenoic acid. While their double bonds help neutralize ROS, a review suggests that omega-3 fatty acids have limited effectiveness in managing dry eye symptoms compared to a control group, indicating the need for further investigation to identify the most effective antioxidant treatments for dry eye disease.[13]

In a model of dry eye illness, recent research shows that melatonin, which is generated by the pineal gland, protects corneal epithelial cells. The role of various hormones, including sex hormones, oxytocin, and growth hormones, has been widely explored in relation to the development of dry eye. These findings provide fresh avenues for examining how hormones contribute to the preservation of the ocular surface. To further understand how unregulated OS leads to the development of dry eye disease and to identify the origins of prooxidants in the condition, more molecular study is required.

2.1.2. Oxidative stress in Keratoconus

KC is a kind of corneal ectasia that affects around 1 in 500 to 2,000 people globally. It is characterized by stromal thinning, central corneal protrusion, astigmatism, and impaired vision. According to recent pathophysiological research, OS is crucial to the processes that underlie KC. Significant cellular stress is seen in the corneal stroma as a result of elevated OS present in conjunction with compromised mitochondrial activity or reduced ROS scavenging capabilities. Unlike traditional theories that link these effects to aging or accumulated DNA damage, this cascade of stress leads to decreased collagen production, loss of keratocytes, and progressive thinning of the cornea.[14] Inflammatory markers such as IL-6, TNF-α, and matrix metalloproteinase (MMP)-9 are notably elevated in the tears of individuals with KC, and their levels show a positive correlation with the severity of the condition.[15]

A key aspect of the pathophysiology of keratoconus (KC) involves disruptions in cellular metabolism and bioenergetics.[16] Changes in metabolite levels associated with fatty acid metabolism, the tricarboxylic acid cycle, and the metabolism of arginine and proline are revealed by metabolomic analysis of stromal tissue from individuals with keratoconus (KC).[17] Corneal fibroblasts from KC patients also exhibit metabolic abnormalities, with reduced arginine levels, increased lactate generation, and changes in cytosolic metabolites linked to glucose metabolism when compared to control samples. Quercetin treatment reduces lactate generation in corneal fibroblasts and influences metabolite levels in glycolysis and the TCA cycle, indicating possible antioxidant advantages. Additionally, quercetin exhibits antifibrotic properties by downregulating the expression of collagen type III and α-smooth muscle actin (α-SMA) in vitro, as well as reducing corneal scarring in vivo.[18] An FDA-approved therapy for KC called riboflavin-mediated crosslinking fortifies the collagen matrix to stop further thinning and stabilises metabolic characteristics. Notable consequences include decreased corneal fibroblast lactate production and lower lactate/malate levels in tears.[19] Exogenous arginine treatment has demonstrated efficacy in addressing certain shortages in procollagen constituents, hence facilitating matrix construction at the cellular level. It is imperative that more study be done on antioxidants and how they affect metabolic processes to promote tissue regeneration. In order to promote optimum wound healing and scarless matrix formation in the setting of KC, this study aims to ascertain if lowering excess ROS in the corneal stroma or causing regulated changes in cellular metabolism during wound healing might aid in minimising fibrotic pathways.[20]

As was previously mentioned, elevated intracellular OS and insufficient antioxidant responses are two of the comparable pathogenic processes seen in both KC and Fuchs' endothelial corneal dystrophy (FECD). OS in the corneal endothelium causes the buildup of aggregated extracellular matrix components called guttae in FECD, which mostly affects the elderly.[21] Severe corneal oedema results from this trend, which also causes the loss of corneal endothelial cells. ROS-induced damage and ultimately endothelial cell death are highlighted by the elevated lipid peroxidation seen in FECD corneal tissue. These results imply that the diminished corneal transparency and notable loss of visual acuity observed in both KC and FECD may be caused by a buildup of OS, whether as a result of decreased antioxidant capacity or increased mitochondrial dysfunction in the corneal stroma and endothelial layer.

2.1.3. Oxidative stress in cataract

The two primary cell types that make up the clear ocular lens, which is situated behind the iris, are elongated lens fibre cells and cuboidal lens epithelial cells. The lens capsule is a thick basement membrane that surrounds these cells. The primary cause of blindness globally is cataracts, which are marked by a loss of clarity in the lens. Cataracts are classified into many categories according to the pathogenic causes and the affected eye component. The most prevalent kind of cataract among all of them is age-related nuclear (ARN) cataract.[22] The majority of cataract treatments available today entail surgery, which has drawbacks. Although surgery significantly improves eyesight in the early stages, 35–40% of individuals eventually acquire secondary cataracts.[23]

One of the main causes of blindness in the globe, cataracts, is largely caused by OS. The clear biconvex

structure of the ocular lens is composed of lens fibre cells (LFCs) and lens epithelial cells (LECs). All enclosed within the lens capsule. Cataracts, which are the primary cause of global blindness, can manifest in different forms depending on their anatomical location and underlying causes.

The lens maintains its functionality and longevity through a delicate balance. While the loss of subcellular organelles enhances its transparency, it also reduces the lens's ability to maintain protein turnover. The lens capsule provides protection against OS, but it may limit the efficient delivery of cellular reductants. Crystallin proteins, abundant in the lens, give it a high refractive index but require sustained solubility to maintain transparency. As lens fiber cells (LFCs) become metabolically inactive with age and lose their ability to synthesize proteins, crystallins undergo post-translational modifications, including oxidation, truncation, glycation, deamidation, aspartate isomerization, and non-disulfide covalent crosslinking. These modifications destabilize crystallins, causing them to aggregate, which is a characteristic feature of age-related nuclear cataract (ARN). Environmental factors such as ultraviolet radiation accelerate this age-related process.[24,25]

Methionine and cysteine oxidation in crystallins, especially in age-related nuclear cataract (ARN), is a major modification. Disulfide linkages are commonly found in the later stages of cataract formation, and deamidation is frequently observed. Both oxidative and non-oxidative modifications, along with amino acid mutations associated with hereditary cataract forms, work together to make crystallins more prone to aggregation.[26]

OS plays an important role in the formation of fibrotic cataracts, including posterior capsular opacification and posterior subcapsular cataract. One important mechanism that results in fibrotic plaques that impair eyesight is the epithelial-mesenchymal transition (EMT). EMT is induced by TGFβ2, which results in cataract development. This is avoided by antioxidants like as glutathione and catalase, and OS and the risk of subsequent cataracts are decreased by lens-specific GSH production deletion.[27,28]

2.2. Oxidative stress and retinal vasculature

One of the tissues with the highest metabolic activity in the body, the retina needs a substantial amount of oxygen and nutrients to continue functioning normally. The choriocapillaris and the central retinal artery system are the two main circulatory networks that guarantee this supply. In order to supply the inner half of the retina, the central retinal arteries give birth to vessels that enter the eye through the centre of the optic nerve and branch into superficial, intermediate, and deep capillary layers. On the other hand, the RPE and photoreceptors are supported by the choriocapillaris, which is situated across from Bruch's membrane. RGCs and pericytes are two of the cell types that work together to generate and maintain the retinal vasculature.[29] By secreting angiogenic factors and intimately interacting with the superficial and intermediate vascular plexuses that supply the GCL, RGCs serve a critical role in preserving vessel integrity.[30] As microcirculation mural cells, pericytes play a crucial role in preserving blood flow, the vasculature, and the blood-retinal barrier. They are essential for the development of the neurovascular unit and react to proangiogenic cues from other cell types and the ganglion cell layer, including RGCs. Pericytes collaborate with glial cells to control retinal blood flow by means of vasodilation and vasoconstriction.[31]

Because of its high metabolic activity, the retina's energy needs are mostly satisfied by oxidative and glycolytic metabolic processes. These processes are further supplemented by nutrients supplied from the retinal vasculature.[32] Retinal glial cells regulate ROS/RNS production; However, these reactive species can build up under pathological circumstances, which might harm the neurovascular unit and exacerbate vascular disorders. For instance, the accumulation of ROS interferes with the metabolism of nitric oxide, which hinders the response of smooth muscle and vascular endothelial cells to changes in blood flow and inflammation. As a result, retinal endothelial cells undergo apoptosis and vascular permeability increases. These effects are linked to various retinal diseases, worsening ROS production and advancing disease progression. The following sections explore severe retinal conditions closely associated with OS.[33,34]

2.3. Oxidative stress during AMD

AMD is a common degenerative disease that mostly affects the retina and causes permanent loss of central vision, especially in elderly people. Because of its large concentration of cone photoreceptors, the disorder primarily affects the macula, an important region in charge of colour vision and fine visual acuity.[35] Advanced age, feminine gender, obesity, genetic susceptibility, a high-fat diet, and smoking are some of the variables that contribute to AMD.[36] Wet AMD involves choroidal neovascularisation, where new, leaky blood vessels form due to VEGF secretion, causing fibrous tissue growth, macular oedema, and haemorrhaging. Dry AMD, which makes up 90% of cases, is characterised by the formation of drusen between Bruch's membrane and the RPE, which causes degeneration of these tissues.[37]

Increased oxygen consumption, exposure to visible light (400–700 nm), and the presence of polyunsaturated fatty acids make the retinal microenvironment very vulnerable to oxidative injury. These fatty acids, along with light-sensitive molecules like lipofuscin and rhodopsin, contribute to the vulnerability of the retina to OS.[38] The aging process diminishes antioxidant capacity, amplifying oxidative components and creating an unhealthy retinal environment. These progressive oxidative changes are crucial in the development of AMD, as increased ROS disrupt lipids,

proteins, and DNA, impairing retinal function. A recent comparative study examining the effects of OS in AMD patients versus non-AMD patients found that AMD patients exhibit upregulation of MDA, 8-OHdG, and protein carbonyls, alongside downregulation of antioxidant isoforms of nitric oxide, including NOS, neuronal NOS, and endothelial NOS, thereby contributing to the development of AMD.[39] Increased nitric oxide levels have the ability to combine with superoxide anions to produce peroxynitrite, which might help the RPE and photoreceptors degenerate by causing protein aggregates to develop between them. When exposed to OS, RPE cells from AMD patients have a decreased ability to upregulate superoxide dismutase (SOD) expression, leading to a greater buildup of ROS in comparison to RPE cells from non-AMD patients. Furthermore, animals lacking SOD1 and SOD2 have elevated ROS levels and characteristics associated with AMD, including choroidal neovascularisation and drusen development.[40,41]

The absorption of UV photons leads to photochemical damage in the mitochondria of the RPE, which increases the production of ROS. In particular, blue light is strongly associated with significant photooxidative stress and ROS generation. The damage caused by light is influenced by several chromophores, such as flavins and porphyrins, which may contribute to the mitochondrial damage induced by blue light.[42] Lutein, a macular carotenoid known for its antioxidant properties, can exhibit prooxidant effects when present at high concentrations. Exposure of blue light to the outer surface of photoreceptors induces OS through the overexpression of NOX family enzymes. Specifically, blue light activates the upregulation of NOX2 and NOX4 enzymes, leading to increased ROS production. This elevated ROS production can be mitigated by the concurrent administration of NOX inhibitors, such as apocynin, which help control the oxidative damage.[43]

Research indicates that cigarette smoking is a substantial risk factor for AMD, with smokers having a 3–5 times higher chance of developing the illness than non-smokers.[44] Smoking contributes to the development of AMD by triggering ROS production, increasing OS through serum lipid peroxidation, and lowering antioxidant levels. Proinflammatory cytokines including C-reactive protein (CRP), which has prooxidative effects on vascular smooth muscle cells, are also elevated. Through NOX-mediated OS, this mechanism increases monocyte adherence to endothelial cells and causes ROS buildup and death.[45,46] In recent research, mice's retinas exposed to vapour from electronic cigarettes showed increased levels of IL-1β, TNFα, and iNOS. Additionally, smoking is associated with a higher genetic risk of AMD, as evidenced by the complement factor H Y402H polymorphism (**Figure 1**).[47,48]

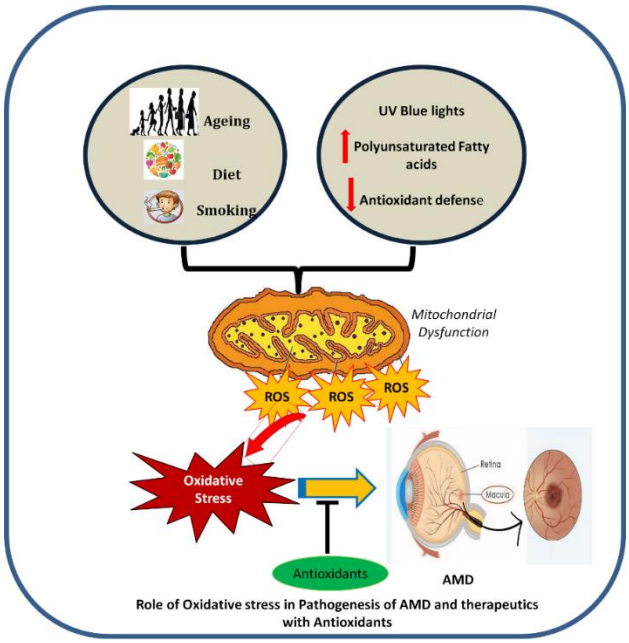

Figure 1: Role of oxidative stress in pathogenesis of AMD and antioxidant treatment

Research suggests that antioxidants should be utilized in models of AMD caused by OS. Zinc, resveratrol, and carotenoids have been recommended as potential treatments for dry AMD.[49] The findings of the Age-Related Eye Disease Study indicate that oral supplementation of antioxidants like Vitamin C, Vitamin E, beta-carotene, and zinc can help slow the progression of AMD. However, subsequent clinical studies, such as the Age-Related Eye Disease Study 2 showed no additional benefits in reducing AMD development with the supplementation of omega-3 fatty acids DHA and EPA, or carotenoids like lutein and zeaxanthin. Vitamin E, known for its ability to reduce lipid peroxidation, continues to offer protective benefits to the RPE.[50] The absence of alpha-tocopherol transfer protein (-TTP), which is essential for maintaining blood levels of Vitamin E, has been linked to retinal degeneration and photoreceptor loss. However, supplementation with Vitamin E has demonstrated a reduction in lipid peroxidation in mouse models of neuronal degeneration. These findings suggest that specific antioxidants may help delay the progression of AMD. Nonetheless, further clinical trials involving larger and more diverse populations are necessary to establish the therapeutic efficacy of these antioxidants and to develop effective preventive interventions for treating age-related retinal degeneration.[51]

2.4. Oxidative stress and glaucoma

Glaucoma, currently the leading cause of irreversible visual impairment worldwide, is expected to increase in prevalence in the coming years. This complex optic neuropathy leads to irreversible blindness by damaging RGCs, which play a critical role in transmitting visual information from the retina to the brain. The condition is typically associated with elevated IOP, although it can also occur with normal or low

IOP. The progressive loss of RGCs and their axons, often before symptoms appear, contributes to the characteristic visual field loss seen in glaucoma. Early detection and intervention are crucial to managing the disease and preventing vision loss.[52] The main contributing factors to glaucoma, such as mechanical stress and reduced retinal blood flow, lead to gradual deterioration of the retina, causing progressive damage to RGCs and their eventual loss. The two most common types of glaucoma, primary open-angle glaucoma and primary angle-closure glaucoma both originate at the iridocorneal angle. Glaucoma's pathophysiology is influenced by various factors, including increased IOP, aging, high glutamate levels, genetic predisposition, alterations in NO metabolism, vascular changes due to retinal ischemia, and OS. RGCs are particularly susceptible to OS because of their high oxygen consumption and abundance of polyunsaturated fatty acids.[53]

Glaucoma pathophysiology is explained by two primary theories: mechanical and vascular, both of which link RGC death to OS. ROS, primarily generated by mitochondria, act as signaling molecules that can trigger apoptotic pathways when present in excessive amounts. Reducing ROS levels may help protect RGCs from apoptosis, which is essential for preserving cellular functions. The mechanical theory focuses on increased IOP, which is considered the primary risk factor for glaucoma.[54] Elevated IOP occurs when there is an imbalance between aqueous humor production and drainage, resulting in direct compression of axonal fibers, deformation of the lamina cribrosa, and disruption of axoplasmic flow, which ultimately leads to RGC death. OS plays a role in damaging the trabecular meshwork (TM), which is located in the sclerocorneal angle and is exposed to light, active mitochondrial activity, and inflammation. The TM, which contains antioxidants for protection, becomes vulnerable to oxidative damage when there is an imbalance in oxidant and antioxidant levels, impairing TM cells through ROS-mediated mechanisms (**Figure 2**).[55]

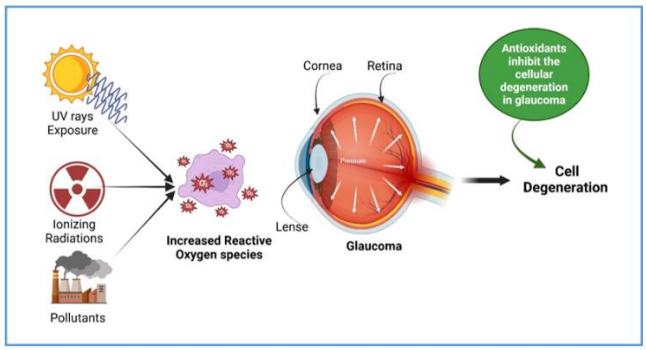

Figure 2: Role of oxidative stress in pathogenesis of glaucoma

The vascular theory emphasizes the reduced blood flow in the retinal vessels, which interferes with the autoregulation of the optic nerve and leads to ischemia-induced production of ROS.[56] Advanced glycation end products, which are OS biomarkers, form through reactions between sugars and amino groups. These products activate signaling molecules, playing a role in immune responses, angiogenesis, and neural apoptosis.[57] OS pathways link both the vascular and mechanical theories in glaucoma. Mechanical compression from elevated IOP impacts blood flow, causing vascular dysregulation, overproduction of ROS, increased expression of OS-related markers, and endothelial dysfunction in retinal arterioles. Additionally, trabecular meshwork (TM) damage, associated with the production of oxidizing free radicals, may contribute to vascular dysregulation.

In glaucoma, OS-mediated pathogenesis may also include inflammation triggered by ROS and glutamate excitotoxicity, independent of IOP or vascular dysfunction.[58] Apoptosis signal-regulating kinase 1 (ASK1)-mediated apoptotic pathways affect TNF-α signaling, a key mediator of neurodegeneration in glaucoma. Deletion of ASK1 prevents RGC death, and its deficiency is associated with lower OS levels, promoting RGC survival.[59]

2.5. Oxidative stress and diabetic retinopathy

DR is the leading cause of acquired blindness among working-age adults in Western countries. It affects approximately 90% of individuals with diabetes, leading to complications that can threaten vision within 25 years of the initial diagnosis. The hallmark of DR is vascular abnormalities, which can be detected using current diagnostic methods. These include microcirculatory issues affecting the eye's capillaries, angiogenesis, and haemorrhaging. These complications, associated with the advanced stages of DR, can lead to retinal detachment and eventual vision loss.[60]

In addition to vascular abnormalities, diabetes causes changes in the neurosensory retina. Before microvascular lesions appear, most retinal neurons and glial cells undergo alterations that worsen as retinopathy advances. These changes include biochemical deficiencies, such as impaired regulation of glutamate metabolism, reduced synaptic activity, and dendritic loss. Apoptosis predominantly affects neurons in the ganglion cell and inner nuclear layers, while microglial cell activation occurs. This activation may help protect the inner retina but also contribute to initiating the inflammatory response.[61]

Recent progress in understanding the pathogenesis of diabetes has strengthened the link between diabetes complications and the severity of hyperglycemia. The Diabetes Control and Complications Trial and the UK Prospective Diabetes Study highlight that elevated blood sugar is the primary factor responsible for the development of DR in both type 1 and type 2 diabetes.[63]

Strict glycemic control significantly reduces the incidence of DR, with four main pathways identified in hyperglycemia-induced tissue damage: the polyol pathway,

the advanced glycation end products pathway, the hexosamine biosynthetic pathway, and the protein kinase C pathway.[64]

A unifying theory suggests that the activation of these pathways is associated with excessive ROS production. Hyperglycemia increases the mitochondrial membrane potential, leading to enhanced superoxide production. It also negatively affects enzymatic components such as SOD, catalase, and enzymes involved in GSH production, further contributing to cellular damage.[65] In addition to increased ROS, there is also an increase in RNS in diabetes. Hyperglycemia induced by diabetes impairs the antioxidant response due to the heightened deterioration within the disrupted metabolic conditions of the disease. The Nrf2 pathway, which is involved in redox balance, inflammation, and proteostasis, plays a crucial role in the pathogenesis of DR.[66]

Antioxidant supplementation has been shown to treat DR by addressing early impairments in the DR neurosensory retina and preventing progression to more advanced stages. Vitamins C and E protected retinal endothelial cells, pericytes, and neural precursor cells from OS in diabetic mice. Additionally, these antioxidants reduced the formation of acellular capillaries and pericyte ghosts.[67] Dietary N-acetyl cysteine supplementation reduced vascular disease in the retina and prevented retinal cell loss and contrast sensitivity impairments in diabetic rats. However, clinical studies have shown no protective effect of β-carotene or vitamins C and E supplementation in patients with DR. Nevertheless, modulating ROS-generating pathways or enhancing antioxidant defense mechanisms remains a promising treatment strategy for diabetes patients.

2.6. Antioxidant therapeutic strategies for eye disorders

Eye disorders, ranging from glaucoma to AMD, DR, and cataracts, are increasingly associated with oxidative stress as a significant contributing factor. Oxidative stress arises from an imbalance between ROS production and the body's antioxidant defense mechanisms. Excessive ROS levels damage cellular components such as lipids, proteins, and DNA, leading to progressive visual impairment. Antioxidant therapeutic strategies aim to counteract oxidative damage, preserve retinal and ocular health, and prevent or slow the progression of eye diseases.[68]

One of the most widely studied antioxidant therapies for eye disorders is the use of vitamins. Vitamin C, a water-soluble antioxidant, plays a crucial role in neutralizing ROS and regenerating other antioxidants such as vitamin E. Vitamin E, a lipid-soluble antioxidant, protects cell membranes from oxidative damage. Both vitamins are particularly effective in managing cataracts and AMD. The Age-Related Eye Disease Study (AREDS) demonstrated that supplementation with a combination of vitamins C and E, beta-carotene, and zinc significantly reduced the risk of advanced AMD progression in patients with moderate to severe forms of the disease.[69]

Lutein and zeaxanthin, carotenoids found in high concentrations in the macula, are another critical focus in antioxidant strategies. These compounds filter harmful blue light and quench ROS, thereby protecting retinal cells from oxidative stress. Studies have shown that dietary supplementation with lutein and zeaxanthin improves visual performance and reduces the risk of AMD. Eggs, leafy green vegetables, and corn are natural sources of these carotenoids.[70]

Polyphenols, a diverse group of plant-based antioxidants, have also gained attention for their potential in treating eye disorders. Resveratrol, a polyphenol found in grapes and red wine, exhibits anti-inflammatory and antioxidant properties that protect retinal cells.[71] It has shown promise in experimental models of DR and AMD by reducing oxidative stress-induced apoptosis and inhibiting abnormal blood vessel formation. Similarly, epigallocatechin gallate (EGCG), the active compound in green tea, has demonstrated neuroprotective effects in glaucoma models by scavenging free radicals and preventing retinal ganglion cell death.[72]

The role of glutathione, a tripeptide and a primary intracellular antioxidant, is critical in ocular health. Glutathione levels are naturally high in the lens and cornea, where it helps maintain transparency and prevent oxidative damage. Depletion of glutathione is associated with cataract formation. Therefore, strategies to boost glutathione levels, such as supplementation with N-acetylcysteine (a precursor to glutathione), have been explored in preventing cataracts and managing oxidative stress in the eye.[73]

Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have anti-inflammatory and antioxidant properties beneficial in eye disorders. These fatty acids are abundant in the retina and play a role in maintaining its structural integrity. Clinical studies suggest that omega-3 supplementation reduces the severity of dry eye disease and may slow the progression of AMD by modulating oxidative stress and inflammation.[74]

Topical antioxidant therapies, such as eye drops, offer a targeted approach to managing oxidative stress. For example, eye drops containing N-acetylcarnosine, a prodrug of carnosine, have shown efficacy in delaying cataract progression by reducing oxidative damage in the lens.[75] Similarly, melatonin, a hormone with potent antioxidant properties, has been investigated for its protective effects against oxidative stress and inflammation in glaucoma.[76]

Emerging strategies involve the use of nanotechnology to enhance the delivery and bioavailability of antioxidants. Nanoparticles loaded with antioxidants such as curcumin and quercetin offer sustained release and targeted delivery, enhancing their therapeutic efficacy. Such advancements

could pave the way for more effective treatments for chronic eye disorders.[77]

In conclusion, antioxidant therapeutic strategies hold great promise for preventing and managing oxidative stress-related eye disorders. By neutralizing ROS, reducing inflammation, and enhancing cellular defense mechanisms, these approaches can significantly improve ocular health and preserve vision. The incorporation of dietary antioxidants, topical therapies, and advanced delivery systems exemplifies a comprehensive approach to combating the debilitating effects of oxidative stress on the eyes. Continued research is essential to optimize these strategies and uncover new possibilities for treating eye disorders effectively.

3. Conclusion

Maintaining redox homeostasis—the delicate balance between antioxidant defenses and reactive oxygen/nitrogen species (ROS/RNS) is crucial for cellular health. When this balance is disrupted, OS occurs, playing a key role in many eye disorders. Both excessive reactive oxidizing species and an overabundance of antioxidants can be harmful, as they function as second messengers in redox signaling. Therefore, antioxidant therapies must carefully maintain the minimum levels of reactive species necessary for normal cellular function.

Ocular tissues contain a variety of cell types with differing levels of mitochondrial activity, leading to varying susceptibilities to OS and distinct antioxidant defense mechanisms. For example, mature lens fiber cells in the lens nucleus have low metabolic activity and lack organelles, while the RPE and photoreceptors, which possess active organelles, contribute to a strong antioxidant defense system. With aging, the increase in reactive oxidizing species and the decline in antioxidant defenses are closely associated with OS in ocular disorders. This age-related shift leads to genetic and epigenetic mutations in DNA, ultimately contributing to the development of various eye conditions.

Mitochondria, which are essential cellular organelles, are particularly sensitive to the effects of aging. Due to poor replication fidelity, a highly oxidative environment, and the lack of protective histones in mitochondria, metabolic changes, cumulative deletions, and mutations accumulate over time. These alterations may contribute to a range of eye disorders affecting both the anterior and posterior segments of the eye.

4. Source of Funding

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5. Conflict of Interest

None.

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