ARTYKUŁ PRZEGLĄDOWY REVIEW ARTICLE

DOI: 10.24292/01.OT.322624

The role of oxidative stress in retinal diseases

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HIGHLIGHTS

Oxidative stress is a common pathophysiological mechanism for age-related macular degeneration (AMD) and diabetic retinopathy (DR). Antioxidant--based therapeutic strategies act as a support of natural protective mechanisms preventing progression and complications of AMD and DR.

ABSTRACT

Oxidative stress plays a key role in the pathogenesis of many diseases associated with aging, including atherosclerosis, neurodegenerative diseases, diabetes, and retinal diseases. The retina is a tissue that is particularly susceptible to the adverse effects of oxidative stress, as it is characterized by high metabolic rate and high oxygen consumption compared to other body tissues. This review article discusses the relationship between the cellular mechanisms of impaired prooxidant-antioxidant homeostasis and the development of age-related macular degeneration and diabetic retinopathy. Natural defense mechanisms of maintaining redox homeostasis and therapeutic strategies based on the use of antioxidants are also described.

Key words: oxidative stress, antioxidants, retina, age-related macular degeneration, diabetic retinopathy

OXIDATIVE STRESS. PATHOPHYSIOLOGY AND TRIGGERS

The formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) is a physiological cellular process that is essential for many metabolic reactions, such as the activation of transcription factors and the regulation of protein phosphorylation processes. ROS and RNS are chemical molecules containing oxygen atoms with an unpaired electron (radicals) or O-O bonds, which are characterized by very high chemical reactivity. Approximately 90% of ROS are produced by the mitochondrial electron transport chain, but they can also be produced by electron chains in the endoplasmic reticulum. The production of ROS/RNS is constantly balanced by an antioxidant defense system against the occurrence of oxidative damage to cellular macromolecules such as nucleic acids, membrane lipids and cellular proteins. In a healthy cell, adequate prooxidant–antioxidant homeostasis is maintained. However, when ROS production exceeds the capacity of the antioxidant defense system, oxidative stress occurs, which contributes to the pathogenesis of many diseases. It has been shown that the severity of oxidative stress increases with age, is closely related to inflammation and immune function, and depends on both genetic and lifestyle factors [1].
The major lifestyle-related exogenous factors that increase oxidative stress include smoking, alcohol consumption, use of certain medications (e.g., non-steroidal anti-inflammatory drugs, doxorubicin, cisplatin, chlorpromazine), infections, antioxidant deficiency and excess of dietary chemical pollutants, radiation, ultraviolet light, environmental pollutants (O_3, NO_3, SO_2), and physical inactivity or overactivity [2, 3]. Advances in medicine, public health and social welfare have led to rapid population growth and demographic changes resulting in a higher percentage of people over the age of 60. In 1950, only 8% of the world's population was over the age of 60. By 2020, the percentage had risen to 13.5% and is expected to reach 28.2% by 2100. The global aging process and the more than threefold increase in the world's population between 1950 and 2020 mean that there are now more elderly people than ever before [4]. One consequence of the aging population is an increased incidence of age-related eye diseases, including age-related macular degeneration (AMD), diabetes, cataracts, glaucoma and dry eye syndrome.

DEFENSE MECHANISMS FOR MAINTAINING REDOX HOMEOSTASIS

To counteract the destructive effects of ROS, cells are equipped with a complex, 3-step antioxidant defense system. The first step involves antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). The second line of antioxidant defense includes low molecular weight antioxidants such as vitamin C, vitamin E, flavonoids and carotenoids. The third line of antioxidant defense is based on the enzymatic removal of oxidized molecules [5].
SOD catalyzes a reaction in which the superoxide anion radical undergoes spontaneous dismutation to hydrogen peroxide and oxygen. Hydrogen peroxide is then removed by CAT and GPx. The proper course of these chemical reactions is ensured by the presence of several cofactors: coenzyme Q10 (ubiquinone), copper, manganese, zinc and selenium. Abnormalities in SOD expression have been implicated in the pathogenesis of many diseases, including neurodegenerative disorders (such as amyotrophic lateral sclerosis), cardiovascular disease, and cancer. Disruption of CAT expression has been associated with Parkinson's and Alzheimer's diseases, schizophrenia, hypertension, and metabolic diseases such as diabetes, vitiligo, and Wilson's disease. GPx plays an important role in the proper functioning of the pancreas and its protection against oxidative stress-induced damage. These observations suggest that GPx plays an important role in preventing the onset of diabetes. In addition, GPx disorders have been found in Huntington's chorea, some cancers and Crohn's disease [5].
Vitamin C is a water-soluble antioxidant that scavenges free radicals and inhibits the peroxidation of lipids, proteins, carbohydrates, and nucleic acids. Ascorbic acid is involved in the regeneration of the hydrophobic antioxidants α-tocopherol and β-carotene from their radical forms. Sources of vitamin C are mainly vegetables and fruits: parsley, blackcurrants, kiwi fruit, red peppers, brassica vegetables, strawberries and citrus fruits [6].
Vitamin E is a fat-soluble organic compound belonging to the tocopherols and tocotrienols. The antioxidant activity of vitamin E is related to the presence of a hydroxyl group in the chromanol ring. α-tocopherols are important components of the lipid membrane and maintain its integrity in the mechanism of inhibition of lipid peroxidation. The main sources of vitamin E are vegetable fats, including wheat germ, sunflower and safflower oils. Vitamin E is found in grain products, nuts, vegetables, meat and dairy products [6]. Flavonoids are a large family of plant polyphenolic compounds consisting of 12 subclasses depending on their chemical structure. The antioxidant properties of flavonoids depend on the number and position of hydroxyl groups, as evidenced by their ability to chelate metal ions with redox activity, such as iron and copper. Mechanisms of ROS inactivation include electron transfer and/or transfer of hydrogen atoms to hydroxyl and superoxide groups, resulting in the formation of less reactive flavonoid radicals [5]. In addition, flavonoids have the ability to modulate cell signaling pathways. Clinical effects include effects on the incidence of cardiovascular disease, cancer and diabetes. The EPIC-InterAct study, which included 16,835 non-diabetic and 12,043 diabetic subjects, found a positive associ-

ation between flavonoid intake and reduced risk of type 2 diabetes [7].

Carotenoids are naturally occurring red, orange and yellow pigments produced by plants, bacteria, fungi and algae. Carotenoids play an important role in neutralizing many ROS (including singlet oxygen) through various mechanisms [8]. Carotenoids can increase the activity of antioxidant enzymes, mainly by activating the nuclear factor erythroid 2-related factor 2 (Nrf2)-dependent pathway [8, 9]. Lutein and zeaxanthin present in the retina absorb nearly 90% of blue light and protect it from light-induced oxidative damage [10].

Heme oxidase (HO-1, hemoxygenase-1) is a key antioxidant that mediates the degradation of endogenous heme protoporphyrin iron. This reaction releases metabolites such as carbon monoxide, iron and biliverdin. The potent antioxidant activity of these metabolites can help defend against peroxides, peroxynitrite, hydroxyl and superoxide radicals. HO-1 is also a key regulator of inflammatory cells. Modulation of HO-1 expression may be a promising therapeutic strategy for age-related eye diseases [11].

AGE-RELATED RETINAL DISEASES

Age-related macular degeneration (AMD) and diabetic retinopathy (DR) are among the age-related retinal diseases based on excessive activation of oxidative stress.

AMD affects 1 in 8 people over the age of 60 and is the leading cause of irreversible blindness in the elderly in developed countries [12]. AMD is estimated to affect 8.69% of the world's population. In 2020, 196 million people had AMD, while the prevalence is expected to increase to 288 million by 2040 [13]. The population of AMD patients is growing steadily, but there are ethnic and regional differences. The prevalence of AMD is estimated to be 12.33% in Europe, 7.38% in Asia and 7.53% in Africa [14]. Another disease whose incidence is associated with age is diabetes. It has been identified by the World Health Organization (WHO) as the epidemic of the 21st century. Based on prevalence data provided by the International Diabetes Federation (IDF), the number of diabetics is expected to increase to 522 million in 2030 and 700 million worldwide in 2045 [15]. DR occurs in approximately 30% of patients with diabetes. After 20 years of diabetes, approximately 99% of patients with type 1 diabetes and 60% of patients with type 2 diabetes have features of DR [16, 17]. What's more, DR is one of the three leading causes of blindness in people of working age, between 20 and 74 years of age [18].

OXIDATIVE STRESS IN THE PATHOMECHANISM OF AMD

AMD is a multifactorial disease in which cellular aging, genetic and environmental factors play a role in its pathogenesis.

The retina is a tissue characterized by high metabolism and oxygen consumption compared to other tissues. In addition, the high concentration of polyunsaturated fatty acids (PUFAs) found in photoreceptor outer segments makes the retina particularly susceptible to oxidative stress-induced damage. PUFAs are particularly sensitive to oxidative stress because ROS initiate the lipid peroxidation (LPO) chain reaction [19]. The retinal pigment epithelium (RPE) is therefore exposed to high concentrations of oxygen and large amounts of ROS. Therefore, efficient repair mechanisms are required to maintain a state of redox equilibrium [1]. In basic research, oxidative stress has been shown to cause both retinal pigment epithelial cell death and subsequent photoreceptor damage during AMD progression. The role of RPE cells is multidirectional; they mediate the transport of nutrients and fluids between photoreceptors and choroidal capillaries, form the outer blood-retinal barrier, and remove photoreceptor outer segments and metabolites. Degeneration or dysregulation of the RPE is a hallmark of AMD pathogenesis. An additional mechanism of the disease is the presence of vascularization defects and subsequent retinal hypoxia. This induces cell death by necroptosis, apoptosis and ferroptosis [1, 3].

Ferroptosis is a newly described form of regulatory cell death characterized by iron-dependent accumulation of lipid hydroperoxides. It has been shown to play a key role in the pathogenesis of AMD [20]. Iron deposition leads to the generation of ROS and oxidative stress in the Fenton reaction, which further promotes lipid peroxidation and subsequent cell membrane damage [21]. In addition, impaired mitochondrial iron metabolism and ROS production have a significant impact on the activation of ferroptosis. Electron microscopic studies have shown that mitochondrial damage in the pigment epithelium is one of the primary pathophysiological features of AMD. Furthermore, the amount of mitochondrial DNA damage and fragmentation in RPE cells correlates with the severity of AMD [22–24].

OXIDATIVE STRESS IN THE PATHOMECHANISM OF DIABETIC RETINOPATHY

One of the major cellular effects of hyperglycemia is the activation of oxidative stress, which leads to the stimulation of a number of pathological pathways, including the activation of vascular endothelial growth factor (VEGF) and a number of pro-inflammatory cytokines, such as IL-1b, IL-6, IL-8, MCP-1 (monocyte chemoattractant protein-1), TNF-α (tumor necrosis factor α), ICAM-1 (intercellular adhesion molecule-1), SDF-1 (stromal cell-derived factor-1) [25, 26]. Retinal vascular endothelial cells are particularly susceptible to this damage, but other cells such as Müller cells, RPE, photoreceptors and pericytes are also affected. At the molecular level, chronic hyperglycemia leads to mitochondri-

al damage and disruption of the ratio of the reduced form to the oxidized form of nicotinamide adenine dinucleotide (NADH/NAD+). This results in the activation of NADPH oxidase isoforms (NOX) and the overproduction of ROS. The latter is responsible for direct damage to cellular structures as well as activation of protein kinase C (PKC), formation of advanced glycation end products (AGEs), increased expression of the AGE receptor (RAGE) and its ligands, and increased flux through the polyol pathway [25–28].

An important aspect of oxidative imbalance is the metabolic memory effect. In clinical practice, this means an increased risk of retinopathy after a transient period of poor glycemic control, even when glycemia is currently under intensive control. In patients, the effect of metabolic memory is evident more than 10 years after the introduction of intensive glycemic control. At the cellular level, oxidative stress, which persists after transient exposure to high glucose concentrations, plays a key role in metabolic memory. This mechanism is regulated by epigenetic modifications, permanent DNA damage in the nucleus and mitochondria, and established perturbations in signaling pathways that control ROS production [29, 30].

THE ROLE OF ANTIOXIDANTS IN AMD

Therapeutic strategies to inhibit oxidative stress include antioxidant supplementation to scavenge ROS and modulation of cell signaling pathways that regulate ROS production and antioxidant defense mechanisms.

The results of prospective, multicenter, randomized, epidemiologic intervention studies suggest an important role for antioxidant supplementation in preventing and inhibiting AMD progression.

An example of research that has significantly changed clinical practice is AREDS/AREDS2 (*The Age-Related Eye Disease Study*). AREDS was conducted on a group of 4757 people and lasted 9 years (since 1992). AREDS2 included a group of 4203 people and lasted 6 years (since 2006). The main finding of these studies is that taking AREDS/AREDS2 formula supplements reduces the overall risk of AMD progression by 25% and by as much as 34% in high-risk groups, including patients with moderately advanced AMD (in one or both eyes) and patients with advanced AMD in one eye (reducing the risk of progression in the other eye) [31, 32]. Table 1 shows the composition of the AREDS/AREDS2 formula.

In a recent Cochrane systematic review published in 2023 (which is an update of a 2017 systematic review), authors Evans and Lawrenson concluded that evidence of moderate certainty suggests that supplementation with antioxidant vitamins and minerals (AREDS: vitamins C, E, β-carotene, copper and zinc) is likely to slow the progression of AMD to late stage disease. People with intermediate AMD benefit more from antioxidant supplements because they are at higher risk of progression than those with early AMD. Studies also support the finding that lutein/zeaxanthin may be a suitable replacement for the β-carotene used in the original AREDS formula. The authors included 26 trials conducted in the USA, Europe, China and Australia. A total of 11,952 persons between the ages of 65 and 75 participated in these studies, with women dominating the study group (56% on average) [33, 34].

The *Women's Antioxidant and Folic Acid Cardiovascular Study* (WAFACS) was a randomized, double-blind, placebo-controlled trial to determine whether a combination of folic acid, vitamin B_6, and vitamin B_{12} could reduce the risk of cardiovascular complications in women with pre-existing cardiovascular disease and at least three risk factors for coronary heart disease. The WAFACS trial began in 1998. 2607 women were enrolled in the folic acid/B_6/B_{12} vitamin group and 2598 in the placebo group. The results showed a statistically significant 35–40% reduction in the risk of AMD in the study group [35].

The CAREDS (*Carotenoids in Age-Related Eye Disease Study*) of the *Women's Health Initiative* (WHI) was designed to evaluate the effects of carotenoids (lutein and zeaxanthin) on the incidence of senile nuclear cataract and AMD. Between 2001 and 2004, 2005 women were enrolled in the CAREDS program. In this study, the risk of AMD was highest in those with vitamin D deficiency and two risk alleles for the CFH (complement factor F) and CFI (complement factor I) genotypes, suggesting a synergistic effect between vitamin D levels and complement cascade protein function. Another 2 conclusions of the study were the effects of lutein and zeaxanthin: these components are moderately associated with a reduced incidence of nuclear cataract in older women, and also have a protective function in the intermediate stage of AMD in healthy women under 75 years of age [36–38].

TABLE 1

The composition of the AREDS/AREDS2 (*The Age-Related Eye Disease Study*) formula.

Supplement	AREDS	AREDS2
Vitamin C	500 mg	500 mg
Vitamin E	400 IU	400 IU
β-carotene	15 mg	-
Copper	2 mg	2 mg
Zinc	80 mg	25 mg
Lutein	-	10 mg
Zeaxanthin	-	2 mg
DHA/EPA	-	DHA 350 mg/EPA 650 mg

DHA – docosahexaenoic acid; EPA – eicosapentaenoic acid.

OTHER ANTIOXIDANT STRATEGIES IN AMD

Risuteganib regulates mitochondrial function and reduces the oxidative stress response to restore the oxidation-reduction balance. It is an anti-integrin peptide that interacts with numerous integrin heterodimers involved in the pathophysiology of AMD. NCT03626636 was a prospective, randomized, double-blind, placebo-controlled, multicenter study comparing the safety and efficacy of a 1.0 mg dose of risuteganib to sham intravitreal injection in patients with intermediate AMD. Risuteganib was found to be a safe drug and no serious adverse events were reported. The study met its primary endpoint with 48% of risuteganib-treated patients (week 28) and 7% of sham-treated patients (week 12) gaining ≥8 letters from baseline (p=0.013). In 2023, the manufacturer, Allegro Ophthalmics LLC, received FDA approval under a Special Protocol Assessment to design a Phase IIb/III clinical trial of risuteganib for the treatment of intermediate AMD.

ALK-001 is a modified form of vitamin A with a deuterium isotope replacing carbon 20 (C20-D3 retinyl acetate or deuterated vitamin A C20). It is designed to reduce the dimerization of vitamin A. The drug, taken once daily in capsule form, replaces natural vitamin A in the body. The SAGA clinical trial, sponsored by Alkeus Pharmaceuticals, Inc., is a double-blind, multi-center, randomized, placebo-controlled clinical trial evaluating the efficacy and safety of ALK-001 in patients with geographic atrophy secondary to AMD. The study is expected to end in the first half of 2024. Results have not yet been reported. Elamipretide has been shown in preclinical studies to normalize mitochondrial structure and function and improve cell function in a broad range of diseases, including cardiovascular, metabolic, neurodegenerative and genetic mitochondrial diseases. Elamipretide readily penetrates cell membranes and localizes to the inner membrane of mitochondria where it interacts with cardiolipin. The ReCLAIM-2 study, sponsored by Stealth BioTherapeutics Inc., evaluated the safety, efficacy and pharmacokinetics of elamipretide in AMD patients with extracapsular geographic atrophy. Treatment consisted of daily subcutaneous injections of 40 mg elamipretide for 48 weeks, followed by a 4-week follow-up period. Results were published in 2023. The drug was beneficial in improving visual acuity and photoreceptor integrity.

DIETARY SUPPLEMENTS IN DIABETIC RETINOPATHY

The results of the study indicate a protective effect of polyphenols in preventing the development of DR. Resveratrol is a non-flavonoid polyphenolic compound that has antioxidant, anti-inflammatory and protective effects on the cardiovascular system. During in vitro studies, it showed neuroprotective effects on retinal ganglion cells and protective effects on the retina and blood vessels against hydrogen peroxide-induced apoptosis. Resveratrol significantly reduces the expression levels of the acetylated proteins NF-κB (nuclear factor κ-light-chain-enhancer of activated B cells), p65 and p53, thus inhibiting oxidative damage, inflammation and apoptosis, the main pathophysiological components of DR [28, 39, 40]. In addition, under the influence of resveratrol, retinal cells in a high glucose environment inhibit the accumulation of VEGF, TGF-β_1 (transforming growth factor β_1), COX-2 (cyclooxygenase-induced 2), IL-6 and IL-8, and suppress the activation of PKC and the degradation of connexin 43. In an animal model, resveratrol reduces retinal vascular permeability and decreases pro-inflammatory cytokines such as IL-1, IL-6, TNF, IFN (interferon), MCP-1, as well as the factors NF-κB, TNF-α and VEGF [39, 41, 42].

Curcumin is another polyphenol with proven antioxidant, anti-inflammatory, anti-tumor, neuroprotective and retinal microcirculatory parameters [42]. At the molecular level, the action of curcumin is multidirectional. It reduces the activity of transcription factors, growth factors, VEGF, and has an anti-inflammatory effect by reducing the expression of TNF-α, IL-1, IL-6, and IL-8. Under hyperglycemic conditions, curcumin activates HO-1 expression by activating Nrf2, thereby counteracting hyperglycemia-induced damage [43].

Other substances with antioxidant activity that show potential positive inhibitory effects on the negative effects of hyperglycemia are: betulinic acid, ferulic acid, the RAGE antagonist group (e.g. TTP488 – azeliragon), the NOX-4 antagonist group (e.g. carotenoids and lowastatin), the Nrf2 activator group (e.g. fenofibrates, maslinic acid). In addition, tricin, urolithin A, quercetin and sulforaphane showed positive effects in cell line studies [28, 42, 44].

Antioxidants have shown significant ROS inhibition in preclinical studies. A number of experiments in cell lines, in vitro and in an animal model of diabetes have clearly confirmed this. In recent years, clinical trials have also been conducted on the use of combination antioxidant therapy in the treatment of DR [28]. However, some of these trials were stopped due to the inability to demonstrate a statistically significant role for antioxidant supplementation in daily clinical practice. The reasons for this situation are multifaceted. One is the complex nature of DR and the heterogeneity of the patient populations. It is worth remembering that a number of risk factors are associated with the development of DR, including duration of diabetes, degree of metabolic control as expressed by glycated hemoglobin (HbA_{1c}) levels, hypertension, hyperlipidemia, pregnancy, low socioeconomic status, ethnicity, older age, kidney transplant status, obstructive sleep apnea, and the presence of nephropathy. The literature also lacks clear bioavailability and metabolism data for individual polyphenols. The final therapeutic concentration in the retina is therefore influ-

enced by a number of factors, from absorption in the gastrointestinal tract, to the composition of the gut microbiome, to transport across the blood-retinal barrier. For example, curcumin has been shown to be synergistic with resveratrol, increasing its absorption by up to 300% [45]. Thus, the combination of polyphenols, as well as the effect of probiotic supplementation, helps to enhance the therapeutic effect [42]. Another issue to consider is the interaction of antioxidants with medications taken by patients for diabetes and its complications. In addition, the role of genetic conditions and environmental factors should be considered. The stage of the disease at which supplementation is initiated and the duration of treatment may also be important.

Research is underway to develop more effective forms of the supplements to increase their bioavailability within the retina. For example, a method of microencapsulation in polymers or the use of gold nanoparticles has been developed for resveratrol [46, 47].

However, there are reports in the literature that provide evidence that complex supplementation targeting oxidative stress mechanisms in patients with diabetes may be of significant supportive value in the prevention of DR. Patients with developed DR may also benefit due to the effective inhibition of retinal lesion progression [48]. In 2011, the results of a 5-year analysis of the role of antioxidant supplementation with lutein, vitamin C, α-tocopherol, niacin, β-carotene, zinc and selenium in more than 100 DR patients were published. The authors showed a delay in the progression of DR, but no significant effect on visual acuity [49]. The premise of the double-blind DiVFuSS (*Diabetes Visual Function Supplement Study*) clinical trial was the use of supplementation with vitamins C, D_3 and E (d-α-tocopherol), zinc oxide, eicosapentaenoic acid, α-lipoic acid, coenzyme Q10, mixed tocotrienols/tocopherols, zeaxanthin, lutein, benfotiamine, N-acetylcysteine, grape seed extract, resveratrol, turmeric root extract, green tea leaves and pycnogenol in patients with DR. The result was an improvement in patients' visual acuity after 6 months of supplementation [50]. An even different approach to the supportive role of supplementation was taken by Lafuente et al. The study included 55 patients with diabetic macular edema treated with intravitreal ranibizumab injections for 3 years. In the study subgroup that received additional oral supplementation with docosahexaenoic acid, there was a more favorable morphologic effect in terms of reduced retinal macular thickness [51].

A systematic review of the role of antioxidant supplementation in DR was published in 2021. The authors included 15 clinical trials that met their inclusion criteria. In their conclusions, they found positive long-term effects in inhibiting the progression of DR in patients undergoing such therapy. This allows us to infer the beneficial effects of its use in daily clinical practice [44].

CONCLUSIONS

Oxidative stress plays an important role in the pathophysiology of age-related retinal diseases such as AMD and DR. The aging of the global population is predicted to increase the incidence of age-related diseases. The complex mechanism of the development and progression of these retinal diseases depends on a number of risk factors that need to be considered in daily patient care.

According to current scientific knowledge and taking into account the convincing results of preclinical and clinical studies, antioxidants can be considered as valuable adjuncts in the treatment of AMD and DR, allowing to halt the progression of the disease and prevent complications.

Further research is underway to determine the optimal composition and ratio of antioxidants, an effective route of administration to ensure bioavailability of the drug in the retina, the most appropriate time to start treatment, and the use of antioxidants targeting specific damage mechanisms in individual patient populations.

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Conflict of interest:
This paper was written in cooperation with Verco.

Financial support:
This paper was written in cooperation with Verco.

Ethics:
The content presented in the article complies with the principles of the Helsinki Declaration, EU directives and harmonized requirements for biomedical journals.