NEC NUTRIMENTUM ET CURAE

Nutr Cur 2023; 02: e136
DOI: 10.57625/nec.2023.41

Eye and nutrition

Maria Cristina Savastano[1,2], Francesco Boselli[1,2], Clara Rizzo[3], Stanislao Rizzo[1,2,4]

[1]Ophthalmology Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.

[2]Università Cattolica del Sacro Cuore, Rome, Italy.

[3]Department of Ophthalmology, Università di Verona, Verona, Italy.

[4]Consiglio Nazionale delle Ricerche, Istituto di Neuroscienze, Pisa, Italy.

Corresponding Author: Francesco Boselli, MD; e-mail: francescoboselli@outlook.it

ABSTRACT

This article highlights the critical role of eye health in overall well-being and the adverse effects of poor eye care, including the development of various eye conditions. It emphasizes the impact of oxidative stress on eye tissues, primarily caused by external factors such as UV light, leading to diseases like dry-eye, cataracts, age-related macular degeneration, and glaucoma. Several nutrients, such as antioxidants, omega-3 fatty acids, vitamins, and minerals, are important in maintaining eye health, particularly in conditions like dry eye syndrome and macular degeneration. Integration of these molecules could be a possible solution for these diseases, like the potential benefits of Mediterranean diets and dietary supplements in preventing eye disorders.

KEYWORDS

NUTRITION

OXIDATIVE STRESS

EYE HEALTH

AGE-RELATED MACULAR DEGENERATION

DRY-EYE SYNDROME

EYE AND NUTRITION

Eye health is one of the aims to achieve general health. Poor eye care can lead to a variety of ophthalmic conditions that impair vision and interfere with day-to-day activities. These illnesses could be mild, with few symptoms like mild discomfort or inflammation. More severe illnesses, however, may eventually cause severe eye damage, a decline in visual quality, or even complete blindness. Common eye disorders that mostly affect older persons, such as cataracts, age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy (DR), are the major causes of vision loss. Although the origins and causes of age-related eye illnesses are varied and complex, one common contributing mechanism has been identified as oxidative stress. The human eye is continually in contact with both artificial and daylight light. Oxidative damage in the ocular tissues is caused by exogenous ROS sources, including UV light, visible light, ionizing radiation, chemotherapy, and environmental pollutants. Apart from directly damaging the tissues, ultraviolet radiation can also cause oxidative stress in the exposed cells by generating riboflavin ROS via the activation of porphyrin and tryptophan, which can then activate oxygen within the cell. Long-term exposure to oxidative stress can result in eye diseases, such as dry eye syndrome (DED), maculopathy or glaucoma. Oxidative stress is defined as an imbalance between the formation of reactive oxygen species (ROS) and the cell's antioxidant capacity. Normal antioxidant defense mechanisms deteriorate in the aging eye and brain and, as a result, in neuro-

degenerative disease, making tissues more susceptible to the damaging effects of oxidative stress. The cornea and the eye's surface shield the other ocular tissues from oxidative stress originating from the environment. Antioxidant enzymes, including glutathione peroxidase, catalase, and superoxide dismutase, normally remove reactive oxygen species produced by oxidative processes[1]. UV rays interact with the cornea's epithelial cells to modify the production of pro-inflammatory mediators and antioxidants. Clinical manifestations of the deterioration of antioxidant defenses in these tissues include the emergence of pterygium, corneal degeneration, and Fuchs' endothelial dystrophy. Because the cells of the crystalline lens and their intracellular proteins are not replenished as they age, the lens is extremely vulnerable to oxidative damage, which can lead to cataractogenesis. Although the trabecular meshwork, the anterior chamber tissue in charge of aqueous humor drainage, has many antioxidant defenses, it is especially vulnerable to mitochondrial oxidative damage, which damages its endothelium and causes malfunction as well as elevated intraocular pressure, which is a sign of glaucoma[2] (Figure 1).

Lastly, dietary antioxidants that delay oxidative damage caused by light, such as macular carotenoids (lutein and zeaxanthin) and vitamins C and E, are especially rich in the retina. For instance, vitamin E spatially distributes in complement with the carotenoid's lutein and zeaxanthin, shields the membranes of the exterior segment of the highly enriched in docosahexaenoic acid photoreceptors, and is regenerated by vitamin C. However, the retina may sustain acute or long-term damage because of oxidative photo stress. Oxidative stress, the death of the retinal pigmented epithelium and the subsequent death of the photoreceptors on top are all involved in the pathophysiology of age-related macular degeneration. As a result, normal antioxidant defense mechanisms in the eye deteriorate with age, just as they do in the case of various neurodegenerative illnesses.

A lower risk of late AMD progression is linked to higher dietary consumption of certain nutrients, such as vitamins, minerals, and carotenoids. Compared to neovascular AMD, these connections are stronger for geographic atrophy, for which there is now no therapy. The same nutrients frequently have protective relationships against the formation of big drusen. Certain nutrient-genotype combinations, particularly those involving omega-3 fatty acids and CFH, have strong genetic connections. These findings might support randomized supplementation trials and additional investigation into underlying mechanisms[3].

One of the primary suspects for damage to mitochondrial DNA (mtDNA) is believed to be free radicals with mitochondrial origins. Mitochondrial dysfunction

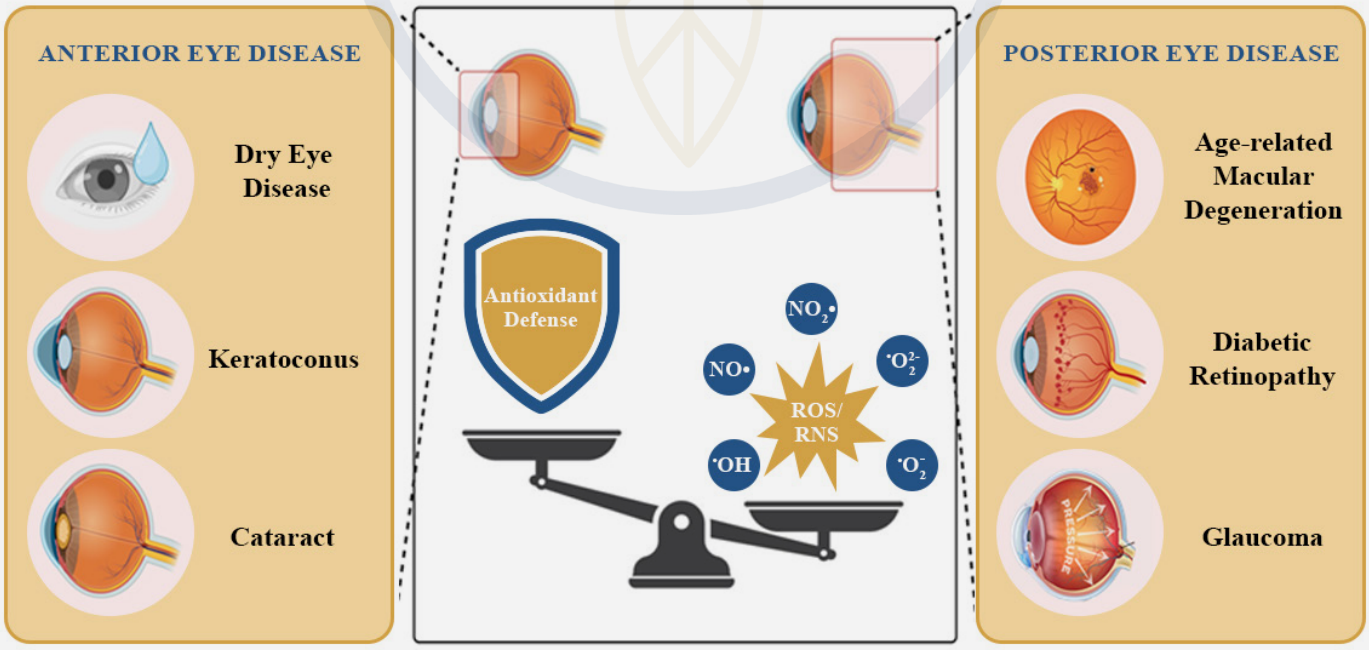

Figure 1. Antioxidant defenses are useful in the protection of diseases of both the anterior and posterior segments of the eye.

results from the production of ROS, which damages the I and III complexes and oxidizes the proteins in the mitochondria and cytoplasm. In several studies, 8-hydroxy-2′-deoxyguanosine (8-OHdG), a biomarker of oxidative DNA damage, has been detected in the mtDNA of the aged brain and in the trabecular meshwork. Furthermore, post-mortem brains of aged adults had significant amounts of 8-OHdG in both nDNA and mtDNA, with glaucoma patients showing greater damage to trabecular mtDNA than healthy subjects. The increased susceptibility of mtDNA to oxidative damage could be attributed to various factors such as insufficient mtDNA repair mechanisms, insufficient protection provided by histone proteins, or the proximity of mtDNA to the internal mitochondrial membrane, which is the site of reactive oxygen species generation (Figure 2).

In this context, prophylaxis and/or therapy of degenerative disorders of the eye appears to benefit from the use of dietary integrators capable of opposing oxidative stress[4].

Several nutrients are important to maintain eye homeostasis and prevent injuries.

Omega-3 polyunsaturated fatty acids (FAs) are essential building blocks of cell membranes and serve as building blocks for the synthesis of a wide range of compounds that have biological activities. Short-chain alpha-linoleic acid (ALA), long-chain eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexanoic acid (DHA) are the primary omega-3 FAs. Long-chain omega-3 FAs are found in oily fish and can be produced by elongating short-chain FAs. Short-chain omega-3 FAs are sourced from plants. The ratio of omega-6 to omega-3 fatty acid consumption affects the biological activity of polyunsaturated fats. Omega-6 FA overconsumption is linked to Western diets; the usual ratio is 15:1, but a 4:1 ratio is recommended.

In addition to regulating lipid metabolism, glucose tolerance, and central nervous system functions, omega-3 FAs have anti-inflammatory, anticoagulant, and antihypertensive properties. These compounds reduce inflammation by competitively inhibiting cyclooxygenase and 5-lipoxygenase, which use arachidonic acid as a substrate. Polyunsaturated fats (FAs) have shown promise in protecting humans against long-term conditions like cancer, heart disease, and neurological disorders[5].

Ophthalmologists are very interested in the potential neuroprotective effects of omega-3 FAs. The formation of tears, the protective blink reflex, and the release of trophic neuromodulators are all dependent on the corneal nerves. Some growing evidence suggests that neurosensory defects may play a part in the genesis of DED and neurotrophic keratitis. A recent clinical trial showed that three months of supplementing with omega-3 FAs led to increased nerve fiber length and branch density in the cornea[6].

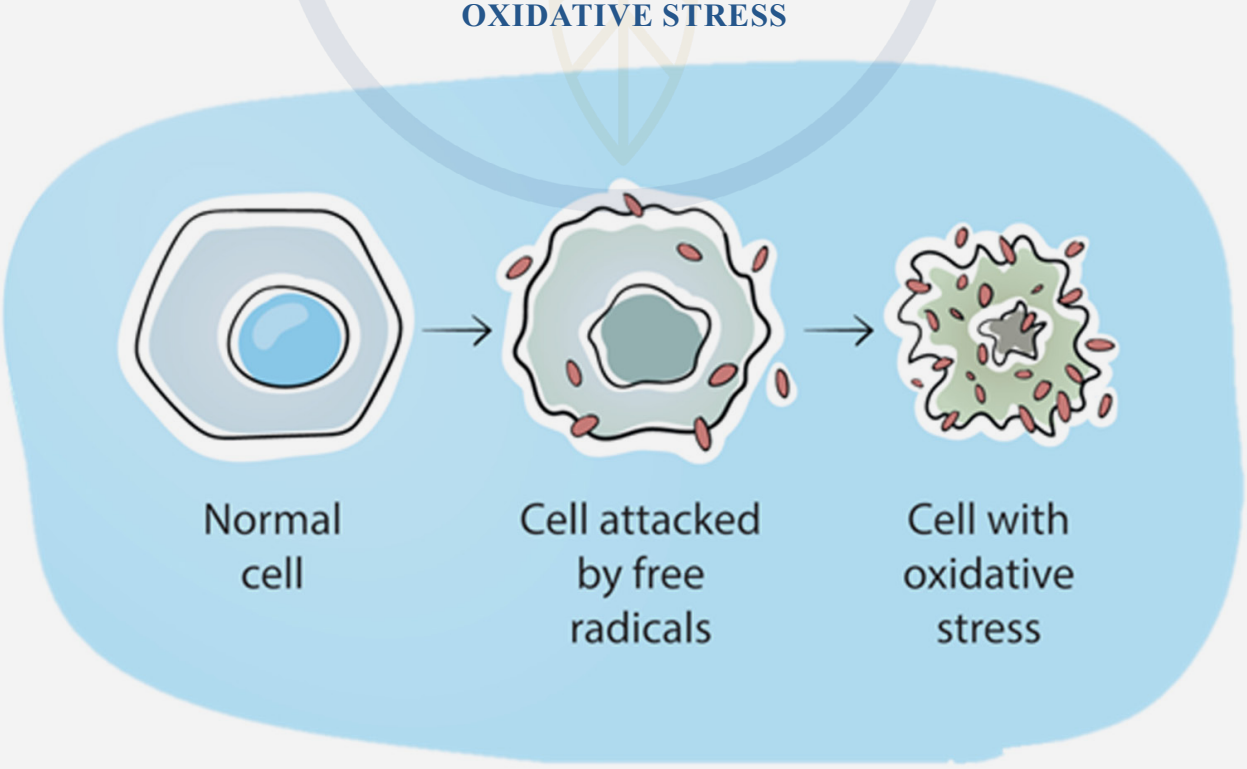

Figure 2. Free radicals induce the production of oxidative damage with alteration of all the cell contents and metabolism.

The most physiologically active form of vitamin A, retinol, is derived from animal sources. Carotenoids, on the other hand, are precursors present in a wide range of fruits and vegetables. Together, they make up the name vitamin A. Mucosal tissues, retinal phototransduction, bone metabolism, reproduction, and immunological function all depend on vitamin A. Specifically, vitamin A plays a role in the development, differentiation, and metabolism of the ocular surface epithelium[7]. Lutein and zeaxanthin are two examples of xanthophyll (oxygen-containing) carotenoids that are selectively concentrated in tissues connected to vision (the brain and eye). Macular carotenoids are thought to reduce light dispersion and shield the retina from light-induced damage by absorbing 40 to 90% of incident blue light, depending on concentration. Additionally, it has been discovered that lutein and zeaxanthin enhance the expression of genes linked to inflammation and inhibit the rise in oxidation-induced cytokines. The risk for AMD is inversely correlated with the levels of lutein and zeaxanthin in the retina. Several studies have shown an improvement in retinal function after dietary supplementation with carotenoids[8].

Furthermore, a decrease in the genetic risk for AMD among people with high lutein and zeaxanthin intake[9]. Nevertheless, a Cochrane review provides evidence that people taking vitamin E or beta-carotene supplements do not reduce their risk of developing age-related macular degeneration[10].

The association between vitamin A deficiency and eye health is very common in the developing world, where one of the main causes of avoidable blindness is vitamin A insufficiency brought on by malnutrition. This situation is rare in Western nations and has been linked to malabsorption diseases such as alcoholism, cystic fibrosis, and bariatric surgery. The first noticeable sign of a vitamin A deficiency is nyctalopia. After starting supplementing therapy in the early phases of insufficiency, visual function typically returns to normal. On the other hand, long-term deficient individuals may experience issues related to the ocular surface, including ulceration, corneal epitheliopathy, and conjunctival keratinization.

In addition to being involved in the metabolism of FA and amino acids, vitamin B12 is a cofactor in DNA synthesis. It is present in animal products such as meat, dairy, eggs, fish, and shellfish, and individuals who consume a vegan diet frequently have deficiencies in it. This vitamin is essential to produce myelin, and its deficiencies have been linked to ocular atrophy, neuropsychiatric disorders, peripheral neuropathy, and myelopathy. Trigeminal, post-herpetic neuralgia, and diabetic neuropathy have all been linked to neuropathic pain that has been treated with vitamin B12. The etiology of DED has come to acknowledge the significance of neurosensory disorders in recent years. Specifically, neuropathic pain resulting from injury to peripheral nerves and/or central sensitization appears to be a prevalent aspect of the illness, potentially explaining the weak association between symptoms and signs found in many DED patients. After receiving vitamin B12 in the form of eye drops or an intramuscular injection, individuals with severe dry eye illness who also had neuropathic ocular discomfort demonstrated improvement in their dry eye symptoms, according to two recent investigations[11]. This shows that the neurosensory defects of DED may be related to vitamin B12 insufficiency.

Water-soluble vitamin C can be found in a variety of fruits and vegetables, including citrus fruits, strawberries, cherries, tomatoes, and broccoli. It is essential for the proper operation of many enzymes. The increased demand for antioxidant protection on the ocular surface is reflected in the high quantities of vitamin C found in the tear film. Moreover, vitamin C appears to be crucial for the processes involved in corneal wound healing.

Vitamin C and E supplements were found to be beneficial in increasing goblet cell density, squamous metaplasia grade, and tear formation and stability in diabetes individuals. This was linked to a notable drop in nitric oxide levels, which might be an indication of how these substances reduce oxidative stress on the ocular surface[12]. The effectiveness of an antioxidant supplementation containing astaxanthin, vitamins A, C, and E, as well as several herbal extracts such Cassiae semen and Ophiopogonis japonicas, in treating individuals with DED was examined in a randomized controlled experiment. The efficacy of the preparation in improving lacrimal gland function, tear film stability, and reducing epithelial damage was confirmed by the significant improvement in objective parameters such as reactive oxygen species tear levels, corneal fluorescein staining, Schirmer test, and tear break-up time after therapy[13]. Antioxidants have been promoted as treatments for delaying and/or prevent cataracts because it is widely known that oxidative damage is a major factor in the etiology of cataracts. As anti-cataract treatments, certain antioxidant interventions, such as vitamin C, have had contradictory outcomes. The possibility that vitamin C-based supplements could postpone the development of cataracts after vitrectomy, which affects up to 80% of patients within two years, is interesting[14].

Vitamin D is a fat-soluble vitamin that can be obtained by eating certain foods or through the skin producing it after being exposed to sunshine. In fact, vitamin D inhibits Th1 and Th2 lymphocyte responses, which has

an immunomodulatory effect. Moreover, it controls cell division, proliferation, and apoptosis, improving the functions of the corneal epithelial barrier. It integrates the lipid component of tear film and tear substitutes by encouraging the formation of surfactants, stabilizing the ocular surface system. Lastly, it regulates the absorption of calcium into the system, which is essential for preserving fluid secretion in the lacrimal and salivary glands. Vitamin D levels in serum have been found to be significantly correlated with tear formation, stability, and symptoms of dry eye syndrome[15].

For these reasons, vitamin D has been researched as a possible DED treatment. Vitamin D deficiency was present in patients with DED refractory to conventional treatment. An integration of Vitamin D was linked with a significant improvement in the Schirmer test, break-up time, corneal staining, eyelid margin hyperemia, subjective discomfort symptoms and corneal stainin[16,17]. Additionally, oral supplementation has been demonstrated to synergistically enhance the efficacy of tear substitutes, and the therapeutic benefit of these products is dependent on serum vitamin D levels.

A tiny group of proteins contains the vital element selenium, which is involved in many processes in living things. Selenium is mostly found in meat, fish, shellfish, and cereals. There are 25 selenoprotein genes in the human genome, and selenoproteins are essential for both human metabolism and embryonic development. Among these, the oxidoreductases thioredoxin reductases, glutathione peroxidases, and iodothyronine deiodinases function best when selenium is available. Glutathione peroxidases catalyze the breakdown of hydrogen peroxide lipid hydroperoxides, which shields cells from oxidative stress. This selenoprotein is widely distributed in many tissues, including the ocular surface, and individuals with DED have lower expression levels of it, which may be a factor in the oxidative damage to the ocular surface. The lacrimal gland produces selenium-transport protein like selenium protein P, which is secreted in tears to supply selenium to the corneal epithelium. Selenoprotein P levels in tears are lower in DED, and oxidative stress is assumed to be elevated due to selenium deficiency[18]. Most of exocrine fluids, including tears, include lactoferrin, an iron-binding glycoprotein that shields the corneal epithelium from UV light. It was shown that DED patients had lower levels of lactoferrin and that giving these patients oral supplements significantly improved their symptoms. Selenium may be a good candidate for clinical use in DED because it supports the manufacture and function of glutathione peroxidases in the cornea, which helps to restore the equilibrium between reactive oxygen species and antioxidant scavengers[1].

Curcuma longa yields the polyphenol curcumin, which is widely used as a spice and flavoring. Curcumin affects several cell signaling pathways, as evidenced by recent, substantial research, and has anti-inflammatory, antioxidant, anti-angiogenetic, wound-healing, and antibacterial properties as a result. The ocular surface system may be subject to pleiotropic effects from curcumin. It suppresses the pro-angiogenic pathway by preventing the proliferation of primary endothelial cells caused by vascular endothelial growth factor and basic fibroblast growth factor, which leads to corneal neovascularization due to inflammation, hypoxia and neovascular AMD. Furthermore, curcumin-mediated stimulation of wound healing has raised the possibility of its use in diseases such as neurotrophic keratitis that are marked by a poor recovery of epithelial integrity. Guo and associates have exhibited the effectiveness of intranasal delivery of curcumin nanomicelle in a mouse model of diabetic keratopathy. By lowering reactive oxygen species, reducing the expression of inflammatory mediators, and raising neurotrophic factors, curcumin helped to restore ocular surface homeostasis[19]. As evidenced by the curcumin-induced down-regulation of pro-inflammatory cytokines, including IL-4 and IL-5 in mouse conjunctiva, curcumin may also have other applications in DED.

A broad class of polyphenols known as flavonoids can be found in red wine, tea, cocoa goods, and many fruits and vegetables. In vitro and in vivo research has shown that flavonoids possess potent anti-inflammatory, immunomodulatory, and antioxidative characteristics[20]. Among the most prevalent and thoroughly researched flavonoids is quercetin. Topical administration of quercetin enhanced goblet cell density, corneal regularity, and tear volume in an experimental mouse model of dry eye. In the lacrimal gland, this was linked to a decrease in inflammatory markers such as MMP-2, MMP-9, ICAM-1, and VCAM[21].

A class of flavonoids called green tea catechins is found in Camellia sinensis leaves, and it has been shown to have anti-inflammatory and antioxidant properties in both vitro and in vivo settings[22]. Epicatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate are the primary catechins found in green tea. Oral treatment of epigallocatechin gallate protected the acinar cells against TNF-α induced cytotoxicity and decreased lymphocyte infiltration in the submandibular glands in a mouse model of Sjögren's syndrome. Epigallocatechin gallate suppressed numerous cytokines generated by IL-1β or hyperosmolarity in human corneal epithelial cells in a dose-dependent manner[22]. Masmali et al[23] assessed how a single green tea intake affected the quantity and quality of tears produced in

persons in good health. Remarkably, after consuming green tea, the tear ferning and phenol red thread tests drastically deteriorated. The authors concluded that green tea's high catechin content might have a deleterious impact on the quality of the tear film. Green tea extract's effectiveness was assessed in 60 patients with DED due to meibomian gland dysfunction using a randomized controlled experiment. In comparison to the control group, the green tea group showed considerably greater improvement in symptoms, break-up time, and meibum quality[24].

All the benefits shown from these molecules have to be linked with the gut. Numerous research have proposed a connection between common eye disorders and gastrointestinal imbalance through immune-mediated ocular reactions[25].

A significant and expanding amount of research suggests that plant-based diets (e.g., the Mediterranean diet, which emphasizes fruits, vegetables, legumes, whole grains, and nuts while limiting animal products and processed foods) can help reduce vision loss caused by AMD, diabetic retinopathy, cataracts, and other eye conditions (Figure 3).

These diets might also be beneficial for other eye disorders[26].

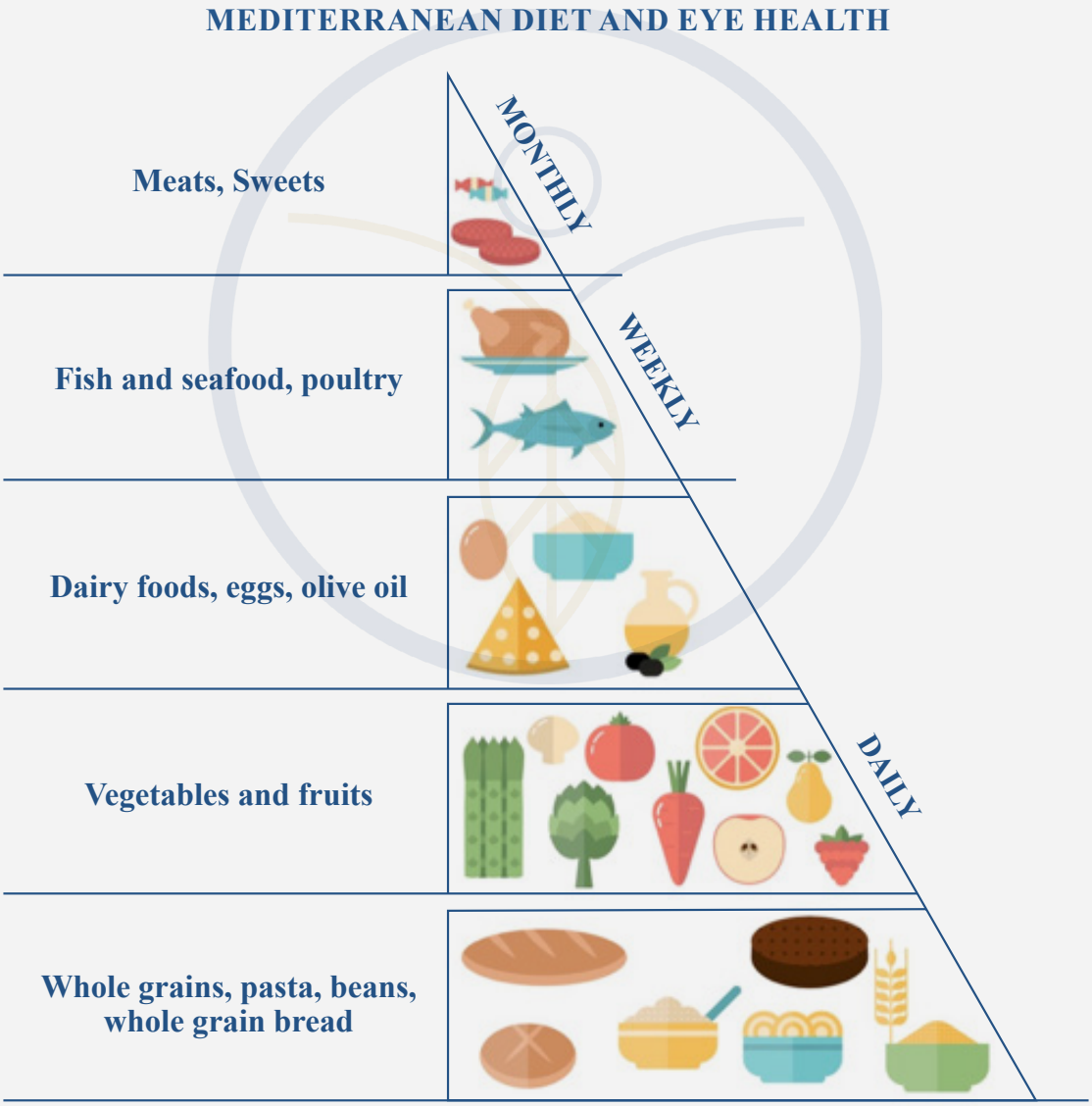

Figure 3. Mediterranean diet mainly based on fruits, vegetables, legumes, whole grains, and nuts while limiting animal products and processed foods, can help reduce vision loss caused by AMD, diabetic retinopathy, cataracts, and other eye diseases.

CONCLUSIONS

A recent Cochrane review[27] indicated with moderate-certainty evidence that antioxidant vitamin and mineral supplementation (Age-Related Eye Disease Study AREDS: vitamin C, E, beta-carotene, and zinc) probably slows down the progression to late AMD. People with intermediate AMD have a higher chance of benefiting from antioxidant supplements because their risk of progression is higher than people with early AMD. Although low-certainty evidence suggested little effect with lutein/zeaxanthin alone compared with placebo, exploratory subgroup analyses from one large American study support the view that lutein/zeaxanthin may be a suitable replacement for the beta-carotene used in the original AREDS formula.

Conflicts of interest

The authors report there are no competing interests to declare.

References

1. Pellegrini M, Senni C, Bernabei F, Cicero AFG, Vagge A, Maestri A, Scorcia V, Giannaccare G. The Role of Nutrition and Nutritional Supplements in Ocular Surface Diseases. Nutrients. 2020 Mar 30;12(4):952. Doi: 10.3390/nu12040952. PMID: 32235501; PMCID: PMC7230622.
2. Saccà SC, Gandolfi S, Bagnis A, Manni G, Damonte G, Traverso CE, Izzotti A. From DNA damage to functional changes of the trabecular meshwork in aging and glaucoma. Ageing Res Rev. 2016 Aug;29:26-41. Doi: 10.1016/j.arr.2016.05.012. Epub 2016 May 27. PMID: 27242026.
3. Agrón E, Mares J, Clemons TE, Swaroop A, Chew EY, Keenan TDL; AREDS and AREDS2 Research Groups. Dietary Nutrient Intake and Progression to Late Age-Related Macular Degeneration in the Age-Related Eye Disease Studies 1 and 2. Ophthalmology. 2021 Mar;128(3):425-442. Doi: 10.1016/j.ophtha.2020.08.018. Epub 2020 Aug 25. PMID: 32858063; PMCID: PMC7902480.
4. Saccà SC, Cutolo CA, Ferrari D, Corazza P, Traverso CE. The Eye, Oxidative Damage and Polyunsaturated Fatty Acids. Nutrients. 2018 May 24;10(6):668. Doi: 10.3390/nu10060668. PMID: 29795004; PMCID: PMC6024720.
5. Wall R, Ross RP, Fitzgerald GF, Stanton C. Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids. Nutr Rev. 2010 May;68(5):280-289. Doi: 10.1111/j.1753-4887.2010.00287.x. PMID: 20500789.
6. Chinnery HR, Naranjo Golborne C, Downie LE. Omega-3 supplementation is neuroprotective to corneal nerves in dry eye disease: a pilot study. Ophthalmic Physiol Opt. 2017 Jul;37(4):473-481. Doi: 10.1111/opo.12365. Epub 2017 Mar 12. PMID: 28295445.
7. Tei M, Spurr-Michaud SJ, Tisdale AS, Gipson IK. Vitamin A deficiency alters the expression of mucin genes by the rat ocular surface epithelium. Invest Ophthalmol Vis Sci. 2000 Jan;41(1):82-88. PMID: 10634605.
8. Moschos MM, Dettoraki M, Tsatsos M, Kitsos G, Kalogeropoulos C. Effect of carotenoids dietary supplementation on macular function in diabetic patients. Eye Vis (Lond). 2017 Oct 15;4:23. Doi: 10.1186/s40662-017-0088-4. PMID: 29046877; PMCID: PMC5641400.
9. Wang JJ, Buitendijk GH, Rochtchina E, Lee KE, Klein BE, van Duijn CM, Flood VM, Meuer SM, Attia J, Myers C, Holliday EG, Tan AG, Smith WT, Iyengar SK, de Jong PT, Hofman A, Vingerling JR, Mitchell P, Klein R, Klaver CC. Genetic susceptibility, dietary antioxidants, and long-term incidence of age-related macular degeneration in two populations. Ophthalmology. 2014 Mar;121(3):667-675. Doi: 10.1016/j.ophtha.2013.10.017. Epub 2013 Nov 28. PMID: 24290803.
10. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. Cochrane Database Syst Rev. 2017 Jul 30;7(7):CD000253. Doi: 10.1002/14651858.CD000253.pub4. PMID: 28756617; PMCID: PMC6483250.
11. Ozen S, Ozer MA, Akdemir MO. Vitamin B12 deficiency evaluation and treatment in severe dry eye disease with neuropathic ocular pain. Graefes Arch Clin Exp Ophthalmol. 2017 Jun;255(6):1173-1177. Doi: 10.1007/s00417-017-3632-y. Epub 2017 Mar 15. PMID: 28299439.
12. Peponis V, Papathanasiou M, Kapranou A, Magkou C, Tyligada A, Melidonis A, Drosos T, Sitaras NM. Protective role of oral antioxidant supplementation in ocular surface of diabetic patients. Br J Ophthalmol. 2002 Dec;86(12):1369-1373. Doi: 10.1136/bjo.86.12.1369. PMID: 12446368; PMCID: PMC1771432.
13. Huang JY, Yeh PT, Hou YC. A randomized, double-blind, placebo-controlled study of oral antioxidant supplement therapy in patients with dry eye syndrome. Clin Ophthalmol. 2016 May 9;10:813-820. Doi: 10.2147/OPTH.S106455. PMID: 27274185; PMCID: PMC4869783.
14. Lim JC, Caballero Arredondo M, Braakhuis AJ, Donaldson PJ. Vitamin C and the Lens: New Insights into Delaying the Onset of Cataract. Nutrients. 2020 Oct 14;12(10):3142. Doi: 10.3390/nu12103142. PMID: 33066702; PMCID: PMC7602486.

15. Yildirim P, Garip Y, Karci AA, Guler T. Dry eye in vitamin D deficiency: more than an incidental association. Int J Rheum Dis. 2016 Jan;19(1):49-54. Doi: 10.1111/1756-185X.12727. Epub 2015 Aug 13. PMID: 26269110.
16. Bae SH, Shin YJ, Kim HK, Hyon JY, Wee WR, Park SG. Vitamin D Supplementation for Patients with Dry Eye Syndrome Refractory to Conventional Treatment. Sci Rep. 2016 Oct 4;6:33083. Doi: 10.1038/srep33083. PMID: 27698364; PMCID: PMC5048427.
17. Yang CH, Albietz J, Harkin DG, Kimlin MG, Schmid KL. Impact of oral vitamin D supplementation on the ocular surface in people with dry eye and/or low serum vitamin D. Cont Lens Anterior Eye. 2018 Feb;41(1):69-76. Doi: 10.1016/j.clae.2017.09.007. Epub 2017 Sep 12. PMID: 28919183.
18. Higuchi A, Takahashi K, Hirashima M, Kawakita T, Tsubota K. Selenoprotein P controls oxidative stress in cornea. PLoS One. 2010 Mar 29;5(3):e9911. Doi: 10.1371/journal.pone.0009911. PMID: 20360971; PMCID: PMC2847950.
19. Guo C, Li M, Qi X, Lin G, Cui F, Li F, Wu X. Intranasal delivery of nanomicelle curcumin promotes corneal epithelial wound healing in streptozotocin-induced diabetic mice. Sci Rep. 2016 Jul 11;6:29753. Doi: 10.1038/srep29753. PMID: 27405815; PMCID: PMC5378915.
20. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. J Nutr Sci. 2016 Dec 29;5:e47. Doi: 10.1017/jns.2016.41. PMID: 28620474; PMCID: PMC5465813.
21. Oh HN, Kim CE, Lee JH, Yang JW. Effects of Quercetin in a Mouse Model of Experimental Dry Eye. Cornea. 2015 Sep;34(9):1130-1136. Doi: 10.1097/ICO.0000000000000543. PMID: 26203745.
22. Cavet ME, Harrington KL, Vollmer TR, Ward KW, Zhang JZ. Anti-inflammatory and anti-oxidative effects of the green tea polyphenol epigallocatechin gallate in human corneal epithelial cells. Mol Vis. 2011 Feb 18;17:533-542. PMID: 21364905; PMCID: PMC3044696.
23. Masmali AM, Alanazi SA, Alotaibi AG, Fagehi R, Abusharaha A, El-Hiti GA. The acute effect of a single dose of green tea on the quality and quantity of tears in normal eye subjects. Clin Ophthalmol. 2019 Apr 10;13:605-610. Doi: 10.2147/OPTH.S201127. PMID: 31040641; PMCID: PMC6462167.
24. Nejabat M, Reza SA, Zadmehr M, Yasemi M, Sobhani Z. Efficacy of Green Tea Extract for Treatment of Dry Eye and Meibomian Gland Dysfunction; A Double-blind Randomized Controlled Clinical Trial Study. J Clin Diagn Res. 2017 Feb;11(2):NC05-NC08. Doi: 10.7860/JCDR/2017/23336.9426. Epub 2017 Feb 1. PMID: 28384900; PMCID: PMC5376801.
25. Russell MW, Muste JC, Kuo BL, Wu AK, Singh RP. Clinical trials targeting the gut-microbiome to effect ocular health: a systematic review. Eye (Lond). 2023 Oct;37(14):2877-2885. Doi: 10.1038/s41433-023-02462-7. Epub 2023 Mar 14. PMID: 36918627; PMCID: PMC10516887.
26. Mulpuri L, Sridhar J, Goyal H, Tonk R. The relationship between dietary patterns and ophthalmic disease. Curr Opin Ophthalmol. 2023 May 1;34(3):189-194. Doi: 10.1097/ICU.0000000000000943. Epub 2023 Mar 1. PMID: 36866844.
27. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Cochrane Database Syst Rev. 2023 Sep 13;9(9):CD000254. Doi: 10.1002/14651858.CD000254.pub5. PMID: 37702300; PMCID: PMC10498493.