Clinical and Experimental Health Sciences

The Role of Omega-3 and Antioxidant Nutrients in Age-Related Macular Degeneration: A Review Article

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ABSTRACT

Abstract Age-related macular degeneration (AMD) is the most common cause of irreversible vision loss worldwide. The cause of the disease is not well explained; studies previse a multifactorial etiology. Various results of studies suggest that omega-3 fatty acids may have beneficial effects in AMD. Besides the omega-3, clinical evidence showed that specific micronutrients (antioxidant vitamins and minerals) protect against AMD. The definition of risk factors for the development and progression of AMD is important for understanding the causes of the disorder and for the determination of its prevention strategies. In this study, the relationship between omega 3 and antioxidant nutrients and the incidence and progression of AMD were evaluated.

Keywords age-related macular degeneration, omega 3 fatty acids, nutrition, dietary supplementations

1. INTRODUCTION

Age-related macular degeneration (AMD) is one of the major causes of irreversible vision loss in the USA, Europe, and other developed countries (1, 2). Approximately 11 million people in the USA and 170 million people worldwide are reported to be diagnosed with AMD, which is expected to reach 22 million in the USA in 2050 and 288 million in the world. AMD prevalence increases with age, and genetic predisposition and environmental factors affect the occurrence of AMD (3-5).

AMD is defined by the existence of specific changes in the macula, notably the deposition of focal yellow extracellular deposits entitled drusen (6). The classification of AMD is divided into dry type (known as nonexudative or non-neovascular) and wet type (known as exudative or neovascular). Dry AMD refers to the presence of drusen in the disease and atrophic variation of dry AMD, where geographic atrophy is prevalent (7). Wet AMD is characterized by the presence of neovascularization within the macula. The developing neovascularization results in hemorrhage and leakage of fluid into the internal retinal layers or subretinal space (8).

Generally, the visual loss in dry AMD develops in years while wet AMD progresses more rapidly. Dry AMD accounts for about 90% of all AMD cases. However, over time exudative AMD type of development is observed in 10-20% of patients. Wet AMD is the type that is observed in quick vision loss (9, 10).

AMD treatment includes medication, smoking cessation, blood pressure control, combined medication, photodynamic therapy, thermal laser photocoagulation, radiation therapy, surgery, and nutrition (11). Laboratory and animal studies indicate that particular micronutrients may have a beneficial effect in filtering short-wavelength light, reducing oxidative stress, inflammation damage, apoptosis, and angiogenesis in the eye. However, clinical and epidemiological studies, which are involved in both interventional and observational studies for dietary nutrients and supplements provide a directly beneficial effect on patients (12). The National Eye Institute of the National Institutes of Health has started The Age-Related Eye Disease Study (AREDS) study as the number of studies investigating the therapeutic effect of nutrition on eye diseases has steadily increased (13). In AREDS and AREDS2 trials, the effect of high-dose antioxidant vitamin combinations (vitamin C, E, beta-carotene, zinc, copper) on the progression of AMD and its association with vision loss were studied. The AREDS formulations consist of pharmacologic doses of vitamins and minerals withstood the recommendations of expert biochemists, ophthalmologists,

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and nutritionists. Although there is consensus on the potential benefits of lutein/zeaxanthin and omega 3, no conclusive results have been obtained for other micronutrients and their combinations. Studies show that vitamin and mineral supplementation with dietary antioxidants (especially lutein and zeaxanthin) could be overtaken by AMD risks (13, 14). There are numerous studies on the intake of dietary carotenoids, antioxidants, and omega-3, which reduce the risk of developing AMD substantially (15-17). The nutrient content of the AREDS and AREDS2 formulations is given in Table 1.

Table 1. *Nutrient content of the Age-Related Eye Disease Study (AREDS) and Age-Related Eye Disease Study 2 (AREDS2) formulation (13, 45)*

Nutrient content of the AREDS formulation			Nutrient content of the AREDS2 formulation	
Nutrient	Daily dosage	% Daily value	Daily dosage	% Daily value
Vitamin C	500 mg	754	500 mg	754
Vitamin E (d-α-tocopherol)	400 IU	1334	400 IU	1334
Zinc	80 mg	464	25 mg	464
Copper	2 mg	80	2 mg	80
Vitamin A (beta-carotene)	28,640 IU	572	15 mg	572
Lutein*	-		10 mg	
Zeaxanthin*	-		2 mg	
Docosahexaenoic acid*	-		350 mg	
Eicosapentaenoic acid*	-		650 mg	

**No daily recommended dietary intake established.*

2. CLASSIFICATION OF AMD

Although there are many classifications of AMD, the classification proposed by the AREDS is now typically used (18-20). There are four stages of AMD progression consistent with clinical examination. A few (<20) medium-size drusen or retinal pigmentary abnormalities are observed in early (dry) AMD. Intermediate AMD is characterized by at least one large druse, numerous medium-size drusen, or geographic atrophy that does not extend to the center of the macula. Advanced or late AMD can be either dry (non-neovascular, atrophic, or nonexudative) or wet (neovascular or exudative). Drusen and geographic atrophy spread out to the center of the macula in advanced dry AMD. Advanced wet AMD is characterized by choroidal neovascularization and its sequelae. Dry AMD accounts for about 80% of cases affecting both eyes. Dry AMD usually slowly progresses and causes only mild loss of vision. But for unknown reasons, it can become a neovascular form of this disease (9).

3. PATHOPHYSIOLOGY OF AMD

The retina changes with AMD is associated with pathological changes in the retinal pigment epithelium, choriocapillaris-choroid complex, and Bruch's membrane (a collagen-rich extracellular matrix between the RPE and choroidal vasculature) (21). Pathogenesis of AMD includes drusen accumulation (extracellular deposits of debris), lipofuscin formation, local inflammation, angiogenesis, and oxidative stress (Figure 1) (22, 23). However, the primary damage of AMD is still unknown, genetic and environmental factors related to primary RPE senescence, alterations in the metabolic pathway, increased inflammation, oxidative stress, imbalance of growth factors, and excessive lipofuscin accumulation may cause harm (24).

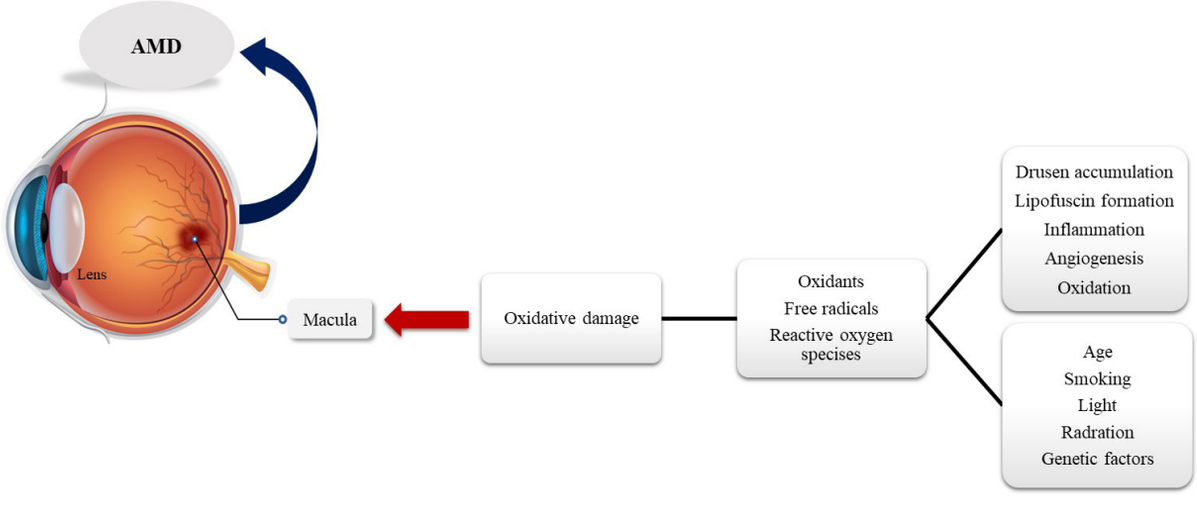


Figure 1. *Pathogenesis of AMD (64)*

There are many risk factors associated with AMD development. Some risk factors, such as family history, ethnicity, gender, cannot be modified, while other risk factors, like smoking, alcohol intake, nutrition, decreased dietary lutein, zeaxanthin, omega 3 and antioxidants, concomitant diseases such as vascular disease, Alzheimer's disease, cardiac disease, and hypertension can be modified (25, 26). The factors that accelerate AMD progression are given in Figure 2.

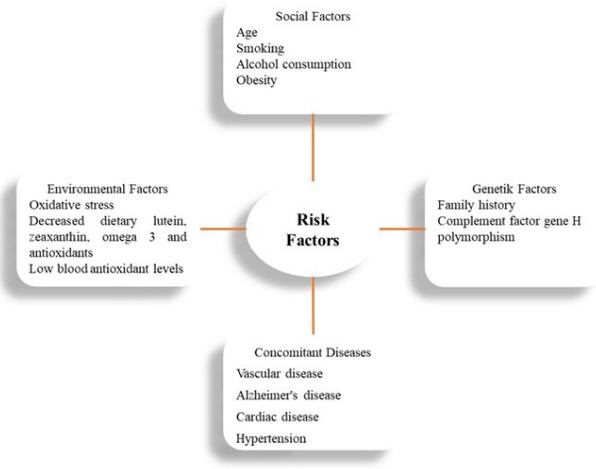


Figure 2. *Factors that accelerate AMD progression (26)*

4. THE MECHANISM OF OMEGA-3 IN AMD

Research has shown that omega-3 fatty acids have potential benefits in patients with AMD and AMD risk (27, 28). Omega 3 is a particularly important component of membrane phospholipids of tissue lipids (29). It is the main fat content of the retina. Omega 3 ensures the fluidity, permeability, and density of the photoreceptor membrane (30). In addition, omega-3 fatty acids can increase the concentration of macular pigment; this pigment is important to filter blue light and locally shows anti-inflammatory and antioxidant activity (31). Dietary omega-3 polyunsaturated fatty acids sources are docosahexaenoic acids (DHA) and eicosapentaenoic acids (EPA). DHA, which transmits visual signals, plays an active role in the regeneration of rhodopsin. Depending on the DHA deficiency, the retinal function has been proven to change. EPA, which is a precursor of DHA, also affects the same metabolic pathway (31-33). EPA and DHA reduce $CD4^+$ T activation and provide an anti-inflammatory environment by transmitting pro-inflammatory into the anti-inflammatory environment. Omega-3 fatty acids can alter inflammation-associated signal cascade and plasma membrane organization by enhancing the molecular organization of lipids and inhibiting lipid seconder messengers, and proteins are needed for activation of T-cells. The anti-inflammatory effect of omega-3 suppresses the formation of new choroidal vessels in exudative AMD (34, 35). Dietary omega-3 fatty acids in the retina macular stimulating the antiangiogenic effect of the derivative is stated to be protective against degeneration (31). Walnut, salmon, sardine, mackerel, flaxseed, flaxseed oil, tuna, and caviar are good sources of omega-3. Omega-3, EPA, and DHA content of walnut, flaxseed, flaxseed oil, and sea products are given in Figure 3 (36).

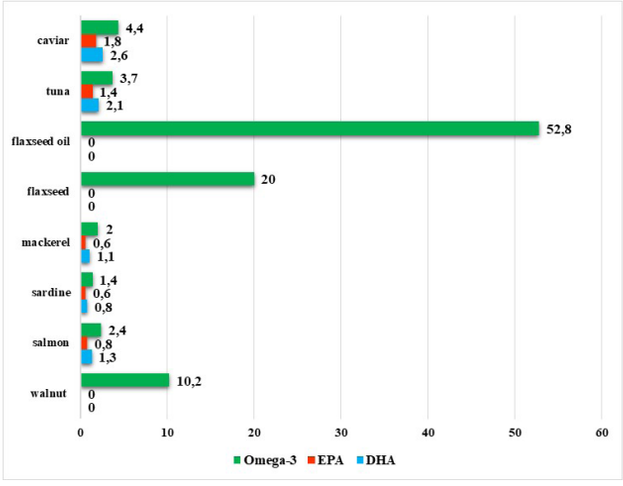


Figure 3. *Omega-3, EPA, and DHA content of foods (g/100 g) (36)*

4.1. Omega-3 Fatty Acids and Fish Intake

The major dietary source of omega-3 fatty acids is fish. The cross-sectional and case-control

studies have shown that EPA, DHA, and fish intake were associated with a significantly decreased risk of incident AMD (37-40).

The AREDS study has been also used to examine the relationship between dietary fat intake and AMD. The AREDS was a double-blind placebo-controlled trial involving 3640 participants from 11 clinics. Omega 3 intakes with patients were estimated by a self-administered semi-quantitative FFQ. The study found that total dietary omega-3 fatty acid intake was inversely related to the incidence of neovascular AMD at baseline (41, 42). In addition, the data obtained from a multivariate analysis of 2132 participants from the AREDS study showed that AMD progression over more than 6 years was inversely associated with EPA or EPA+DHA intake (41).

In The Blue Mountains Eye Study, the relationship between dietary fatty acid intake and AMD development risk within 10 years was evaluated. According to the results obtained from the study, 1 serving of fish per week was associated with a reduced risk of an incident early AMD (RR, 0.69, 95% CI, 0.49-0.98). Similar to the fish intake, 1 to 2 servings of nuts per week was associated with a reduced risk of the incident early AMD (RR, 0.65, 95% CI, 0.47-0.91) (43).

In the meta-analysis and systematic review of prospective cohort studies, once per week fish consumption significantly decreased the risk of AMD (RR, 0.89, 95% CI, 0.83-0.96). Analysis by fish type showed that dark meat fish (RR, 0.68, 95% CI, 0.46–0.99), especially tuna fish (RR, 0.58; 95% CI, 0.47–0.71) intake, was associated with reduced AMD risk (44).

4.2. Omega-3 Supplementation

The AREDS2 is one of the most important randomized, double-blind controlled trials which investigated the effect of omega-3 in the prevention of AMD. The AREDS2 tried to determine the effect of the addition of the carotenoids lutein and zeaxanthin, the omega-3 fatty acids on the risk of developing advanced AMD and/or moderate vision loss in people at moderate to high risk for progression. Similar to AREDS, AREDS2 was a multicenter, double-blind, placebo-controlled trial. It included 4203 patients between the ages of 50 and 85 who had intermediate AMD according to the classification system described for AREDS. The results of the study showed that omega 3 did not prevent the development of AMD (45).

The nutritional AMD Treatment 2 (NAT-2) study is another randomized, case-controlled study to evaluate the efficacy of DHA-enriched oral supplementation (840 mg/day DHA and 270 mg/day EPA from fish oil capsules) in preventing exudative AMD (46). The incidence of neovascularisation was not significantly different when the DHA-enriched supplemented group was compared with the placebo group. However, the study mentioned that the DHA-enriched supplemented group had a significantly lower risk of developing neovascularization in red blood cells membranes over 3 years.

Patients with dry AMD were given omega-3 supplements (3.4 g EPA and 1.6 g DHA) for 6 months. There was a significant improvement in visual acuity in all patients within the fourth and sixth months after omega-3 supplementation (47). In the LUTEGA study, individuals were divided into 3 groups, and the first group (D1) was given supplements containing 10 g lutein, 1 mg zeaxanthin, 100 mg DHA, 30 mg EPA and antioxidant once a day; the second group (D2) was given supplements containing 10 g lutein, 1 mg zeaxanthin, 100 mg DHA, 30 mg EPA and antioxidant twice a day, and the third group was given placebo (P). The volume of macular pigment optical density increased significantly in D1 and D2 and decreased significantly in P. Best-corrected visual acuity improved significantly in D1and D2 groups at the end of 12 months compared with the P (48).

Despite similar main results, the studies have methodological differences. The formulations of supplements (e.g., DHA / EPA ratio), duration of the study, sample size, nutritional parameters of patients (e.g., serum DHA / EPA), and bioavailability of supplements (e.g., ethyl-esters form or triglyceride form) are among the differences of the studies. There is a need for detailed and comprehensive studies using different formulations.

In addition to the protective effect of omega-3 fatty acids on AMD, the omega-6/omega-3 ratio is important. Čaljkušić Mance et al. suggested that decreased omega-6/omega-3 ratio protects against neovascular AMD. The data showed that the dietary omega-6/omega-3 ratio in patients with neovascular macular degeneration was about 11/1, while this ratio in mild and moderate form AMD was about 7-7.5/1, and the control group was about 7/1 (49).

These results support the hypothesis that omega-3 fatty acids could prevent or delay the onset of macular degeneration. While increasing the intake of omega-3 rich nutrients in the diet, it is important to consider the omega-6/omega-3 ratio as well (50).

5. ANTIOXIDANT NUTRIENTS AND AMD

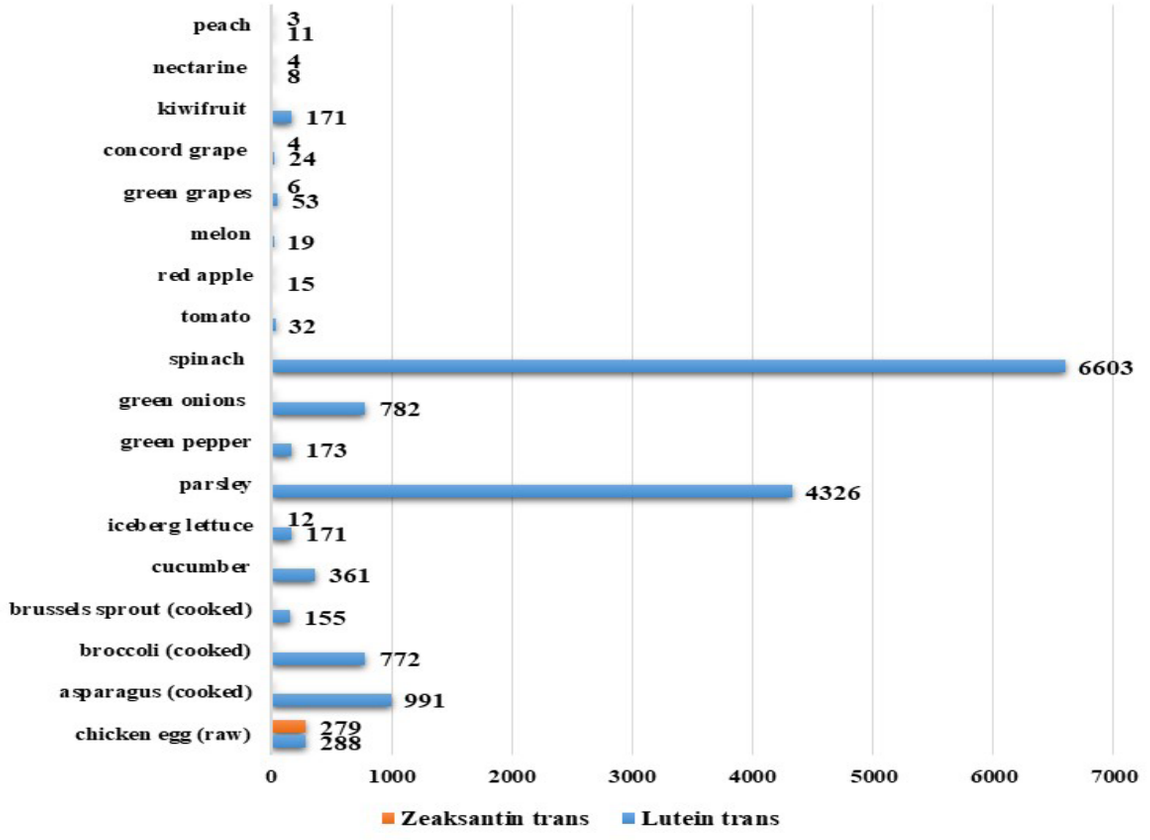
Oxidative stress, which refers to cellular damage caused by reactive oxygen species, has been supposed to contribute to the development of AMD (51). Oxygen consumption of the retina is higher than many other tissues, and the retina is exposed to intense light conditions. Retinal constituents are rich in polyunsaturated fatty acids that oxidize easily, and retinal pigment epithelium contains an excess of photosensitizers. The reasons cited are the formation of reactive oxygen species in the retina and the development of oxidative damage (52).

As oxidative stress could cause the accumulation of drusen, intake of antioxidants with diet or supplements may be beneficial in AMD. An appropriate diet or supplementation with vitamins, minerals, and carotenoids can prevent the development and progression of AMD (53, 54).

5.1. Carotenoids

Although there are more than 600 varieties of carotenoids, 6 carotenoid species are found in diet and serum: lutein, zeaxanthin, α-carotene, β-carotene, lycopene, and β-cryptoxanthin (55). Lutein, zeaxanthin, and their common metabolite are known as meso-zeaxanthin macular pigments (56). Meso-zeaxanthin comes from the lutein and zeaxanthin pigments in the yellowish color structure of the macula. Lutein and zeaxanthin protect the retina against photo-oxidative damage (57, 58). Several studies determined that a higher intake of carotenoids in diet, especially lutein/zeaxanthin, was associated with a lower risk for AMD (16, 55, 59). In the AREDS study, supplement formulation containing antioxidant vitamins (vitamin E, C) and minerals (zinc and copper) and β-carotene but not lutein and zeaxanthin reduced the risk of AMD progression (13).

It should be noted that high beta carotene intake can cause lung cancer in smokers. Results of the prospective cohort studies on this subject are needed (12). Lutein and zeaxanthin content of the chicken egg, some fruits, and vegetables are given in Figure 4.



For all foods, it is the predominant form of xanthophylls trans isomeric forms.
***Figure 4**. Lutein and zeaxanthin content of foods (µg/100 g) (36)*

5.2. Vitamin C

Vitamin C is an important water-soluble antioxidant. It supports the regeneration of vitamin E (60). In a population-based cohort study, it was reported that vitamin C intake was not associated with AMD (61). In a systematic review of five studies searching for antioxidant supplements in the development of AMD, there was no evidence that vitamin C prevented or delayed the onset of AMD (62).

5.3. Vitamin E

Vitamin E is a lipid-soluble antioxidant that maintains the cell membrane by scavenging the reactive oxygen species (63). A case-controlled study was conducted with people aged ≥ 50 years, and it revealed that a high dietary intake of vitamin E was found to substantially reduce the risk of developing AMD (64). The Rotterdam study also showed a decreased risk for AMD in subjects with high dietary intakes of vitamin E, but a prospective randomized placebo-controlled trial showed that daily vitamin E supplements did not prevent the development or progression of early/late stages of AMD (65). At the same time, vitamin E supplementation has an anticoagulant effect and may cause heart attacks. There are studies suggesting that an increase in vitamin E intake increases the risk of prostate cancer (66, 67)

5.4. B Vitamins

High plasma homocysteine concentrations cause vascular endothelial dysfunction that induced the development of AMD. Several studies show the relationship between plasma homocysteine levels and AMD risk. A meta-analysis of eight homocysteine-lowering trials showed that vitamin B_6 and vitamin B_{12} and folic acid reduced homocysteine levels (68), and vitamin B_6 and vitamin B_{12} improved endothelial dysfunction (69). In a randomized, double-blind, placebo-controlled study with females, combined folic acid, vitamin B_6, and vitamin B_{12} therapy was associated with a 34% lower risk of AMD and a 41% lower risk of visually significant AMD (70). B vitamins both reduce the levels of homocysteine and protect the blood vessels in the eye by creating an antioxidant effect.

5.5. Zinc

Zinc has antioxidant functions and acts as a cofactor in several enzymes (e.g., retinol dehydrogenase, superoxide dismutase) (71). The retina contains high amounts of zinc; therefore, zinc is an important mineral for the optimal metabolism of the eye (72).

In the AREDS clinical trial, patients were divided into 4 categories based on disease severity. The first group received antioxidant daily oral tablets which contained vitamin C 500 mg; vitamin E (as d-α-tocopherol) 400 IU; beta carotene 15 mg, the second group was given zinc 80 mg (as zinc oxide) and copper 2 mg (as cupric oxide) the third group was given antioxidants+zinc; the fourth group was given a placebo. The results revealed that the risk of AMD progression was reduced by 25%. No such reduction was detected in antioxidant vitamins alone (12). However, compared to high-dose (80 mg) in the AREDS2 study (45), no significant benefit was found in low-dose zinc (25 mg), Findings of the Rotterdam Study showed that dietary intake of zinc was inversely associated with incident AMD and reduced the risk of AMD in elderly people (73).

6. CONCLUSIONS

The risk of AMD is increasing all over the world. In particular, exudative AMD gives rise to the types of irreversible vision loss. The results of studies suggested that there was a positive effect of dietary omega-3 and lutein/zeaxanthin intake on the development and progression of AMD. To reduce the incidence and severity of disease, it is necessary to increase the intake of omega-3, lutein/zeaxanthin by the age group and requirements of the individual's diet. Dietary sources of omega-3 are oily fish, seafood, walnut, flaxseed, and their oils. Lutein and zeaxanthin are obtained from green leafy vegetables (peas, spinach, kale, lettuce, and broccoli), carrots, eggs, and cheese. To increase the dietary omega 3 intakes, nutritionists recommend that fish be consumed twice a week (500 g). Regarding antioxidant micronutrients, only the AREDS 2 formulation can currently be recommended to patients for reducing the risk of AMD.

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Conflict of interests

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Author Contribution *(Authors initials)*

Research idea: EK

Design of the study: EK, NAT

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Revising it critically for important intellectual content: NAT

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