Antioxidant supplements in age-related macular degeneration: are they actually beneficial?

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Abstract: Age-related macular degeneration (ARMD) is one of the prominent causes of central visual loss in the older age group in the urbanized, industrialized world. In recent years, many epidemiological studies and clinical trials have evaluated the role of antioxidants and micronutrients to prevent the progression of ARMD. In this article, we review some of these major studies. In addition, we review the absorption and bioavailability and possible undesirable effects of these nutrients after ingestion. The role of genotypes and inappropriate use of these supplements are also discussed. From all the above evidence, we conclude that it may not be prudent to prescribe these formulations without a proper assessment of the individual's health and dietary status. The effectiveness of all the components in antioxidant formulations is controversial. Thus, these supplements should not be prescribed just for the purpose of providing patients some kind of therapy, which may give a false sense of mental satisfaction.

Age-related macular degeneration (ARMD) is one of the foremost causes of central visual loss in the older age group in the industrial world affecting 10% of people above 65 years and more than 25% of people above 75 years of age.[1] Progressive visual loss in ARMD has been attributed to the late-onset neurodegeneration of the photoreceptor–retinal pigment epithelial complex in the macular area.

In recent years, many epidemiological studies and clinical trials have been conducted to assess the role of antioxidants and micronutrients in delaying the progression of visual loss in patients suffering from ARMD. AREDS (age-related eye disease studies) has been one of the major clinical trials highlighting the effectiveness of antioxidant supplements in ARMD, and thereafter, numerous primary studies and review papers have suggested a positive association between antioxidant supplements and a decrease in progression of ARMD,[2–9] making it a promising strategy for slowing the progression of the disease. A common

trend of self-medicating has been noted without taking into consideration the correct ingredients and the proper dosage, which are almost always available over the counter without a prescription.

Review of literature

Literature searches of the PubMed and Cochrane Library databases were last conducted on 3 November 2020, with no date restrictions. The keywords used while searching the PubMed database were: "role of antioxidants in ARMD," "bio-availability and absorption of" (individual components of antioxidant formulations), "side effects of" (individual components in antioxidant formulations), "composition of" (different antioxidant formulations available in the market). Further details regarding side effects of antioxidant supplements were explored with the keywords "association of" / "role of" (particular micronutrient) "with" (particular disease/side effects described). The National Institutes of Health (NIH) website was also visited to confirm

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the recommended dose allowances of various micronutrients. All our searches were limited to articles published in English language. Our data are based on both primary studies and review articles focussed on the metabolism of the micronutrients in antioxidant supplements to highlight the factors associated with their absorption and bioavailability.

Besides AREDS, few other major studies evaluated the effectiveness of antioxidants in the prevention of development or progression of ARMD. Cochrane Database of Systematic Reviews[10–12] has studied the role of antioxidant supplements in ARMD extensively, and the results are tabulated in Table 1.

Before dwelling on the effectiveness of these antioxidants and micronutrients, let us also review the absorption and bioavailability of these nutrients after ingestion.

Absorption and bioavailability of micronutrients and antioxidants

Zinc
Zinc is one of the most important constituents of antioxidant supplements recommended in a dosage of 80 mg of elemental zinc in the form of zinc oxide by AREDS2. Zinc is an essential co-factor for various metabolic activities in the eye and plays an important role in physiological processes such as immunity, reproduction, and neuronal development.[13,14] A high concentration of zinc has been observed in the retina and retinal pigment epithelium (RPE), which helps in modifying photoreceptor plasma membranes, modulating synaptic transmission, and regulates the phototransduction pathway.[13,15]

Absorption of exogenous dietary zinc. A carrier-mediated process in the small intestine is involved in zinc metabolism.[16] It is difficult to estimate the proportion of dietary zinc absorption because secretions from the gut also contain zinc. The absorption rate of zinc depends on a variable range of factors such as stress, alcohol consumption, caffeine, drug intake, exercise, diet, and phytate: zinc molar ratio.[17] An increase in dietary zinc consumption increases zinc absorption up to a maximum rate.[17,18] The zinc status of the host determines the rate of zinc absorption. Increased efficacy of absorption has been observed in zinc-deprived individuals and *vice versa*.[19]

A dynamic relationship has been observed between absorbed zinc and intestinal excretion. A compensatory reduction in the amount of zinc excreted *via* the intestine has been noted when absorption is low and *vice versa*.[20] Therefore, intestinal regulation of endogenous zinc excretion plays an important role in zinc homeostasis. Istfan and colleagues[21] observed zinc absorption of 92% in young men fed with a low-zinc diet and 81% in those fed with a high-zinc diet.

Bioavailability of exogenous dietary zinc. Bioavailability of zinc is dependent on dietary factors and physiological factors such as mucus layer and intestinal fluid.[22] Phytate remains the main nutritional inhibitor of zinc bioavailability and alteration in human zinc absorption pattern is observed beyond molar phytate: zinc ratio of 5.[22] Dietary protein (especially from animal sources) increases the bioavailability of zinc by forming complexes with zinc, which facilitates solubility of the cation in the intestinal lumen.[23] Calcium also has a possible negative impact on zinc bioavailability.[22] Albumin concentration on the serosal side of the intestinal epithelium is another determinant factor of zinc bioavailability having a high zinc affinity and acts as a binding and transport protein.[22,24]

Thus, adding Zinc to the diet of people who are not malnourished may not actually enhance its blood levels and availability to retinal tissue.

Xanthophylls
Lutein and zeaxanthin are two dietary xanthophylls recommended in a dosage of 10 mg and 2 mg, respectively, by AREDS. Lutein and zeaxanthin are short-wavelength light filters that preserve the redox balance in the body.[25] Green leafy vegetables and fruits are the main sources of lutein and zeaxanthin. Studies have documented a positive role of these xanthophylls in the prevention of progression of ARMD. The bioavailability of lutein and zeaxanthin, however, is dependent on variable factors, which should be taken into account while prescribing supplements.

Absorption of dietary xanthophylls. It involves four major events: release of the xanthophylls from the food matrix, transfer of the released particles to lipid micelles in the small intestine (facilitated by dietary fat intake and biliary secretions), uptake by the intestinal cells *via* passive diffusion, and transportation to the lymphatic system.[26,27]

Table 1. Summary of Cochrane database of systematic reviews on the role of antioxidant supplements in ARMD.

Study	Aim	Methodology	Results
1. *Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration*[6]	Assess whether antioxidant vitamin and mineral supplements prevent the development of ARMD in healthy people in the *general population*	5 relevant studies were included (total of 76,756 people)—in Australia, Finland, and the United States. They compared vitamin C, vitamin E, β-carotene, and multivitamin supplements with placebo.	Taking *vitamin E/vitamin C/β-carotene supplements made little or no difference to the chances of developing ARMD* (high-certainty evidence). Taking *multivitamin tablets may slightly increase the chances of developing any ARMD or late ARMD* (moderate-certainty evidence).
2. *Antioxidant vitamin and mineral supplements to slow down the progression of age-related macular degeneration*[7]	Assess the effects of antioxidant vitamin or mineral supplementation on the *progression of ARMD in people with ARMD*.	19 studies conducted in the United States, Europe, China, and Australia. Compared antioxidant vitamin or mineral supplementation (alone or in combination) with placebo or no intervention, in people with ARMD.	Taking *lutein alone (or combined with zeaxanthin) may have little or no effect on progression to late ARMD* and vision loss (low-certainty evidence). Taking *vitamin E alone may have little or no effect on the progression to late ARMD* and vision loss (low-certainty evidence). Taking antioxidant vitamins plus zinc probably slows down the progression to late ARMD and vision loss (moderate-certainty evidence). This may result in a small improvement in quality of life (low-certainty evidence).
3. *Omega 3 fatty acids for preventing and slowing the progression of age-related macular degeneration*[8]	Whether increased dietary intake of omega-3 fatty acids prevented or slowed the progression of age-related macular degeneration	Randomized controlled trials where increased dietary intake of omega-3 fatty acids was compared with placebo or no intervention. People from the general population were recruited with or without ARMD. Any type and any dose of omega-3 fatty acids, either as fish oil capsules or dietary manipulation (e.g. increased consumption of oily fish).	Omega-3 supplementation for periods up to 5 years *did not reduce* the rate of progression to advanced ARMD or reduce significant visual loss compared with a placebo. The incidence of adverse effects was similar in the intervention and placebo groups. *Omega-3 supplementation in people with ARMD does not reduce the risk of progression to advanced ARMD or the development of moderate to severe visual loss.*

ARMD: age-related macular degeneration.
High certainty: very confident that the true effect lies close to that of the estimate of the effect; moderate certainty: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low certainty: the true effect may be substantially different from the estimate of the effect; very low certainty: The true effect is likely to be substantially different from the estimate of effect.

Roodenburg and colleagues[28] reported that more than 3 g of fat was required to enhance the solubility of lutein diesters and facilitate pancreatic secretions of lipases and esterases. Lutein diesters being hydrophobic requires fat and hydrolysis by pancreatic enzymes to make them soluble.[28]

Bioavailability of xanthophylls. Olive oil (monounsaturated fatty acid) can improve lutein bioaccessibility and bioavailability by regulating the activity of intestinal lipases in mice with a lutein-deficiency state.[29] Highly saturated-fat containing butter and palm oil are better enhancers of

xanthophyll bioavailability than oils with high polyunsaturated fatty acid (PUFA) content.[30] Egg yolk is a better source of zeaxanthin than oral supplements.[31] Thus, it is also important to assess the type of fat intake of an individual before prescribing these xanthophylls.

Vitamin A

It is an essential micronutrient for cell growth and differentiation, immunity, and preserving vision.[32] Animal-based foods [containing preformed vitamin A in the form of retinyl esters (REs)] and fruits and vegetables (enriched with provitamin A carotenoids) are the natural sources of Vitamin A. Increased amounts of dietary vitamin A intake has been proven to be associated with decreased risk for any stage of ARMD.[33,34] A recommended daily intake of 700 μg/day of REs for men and 600 μg/day of REs for women has been observed to protect from macular degeneration and associated complications.[35] Other epidemiological studies, however, could not find any association between dietary intake of vitamin A and reduced risk of ARMD and its progression.[7,36]

Digestion and absorption of exogenous preformed vitamin A. During the process of digestion, fat-soluble vitamin A is incorporated with other lipids into mixed micelles, which is presumably necessary for absorption by the enterocyte. Incorporation of the vitamin A particles into the micelle during dietary lipid lipolysis by gut lipases is affected by several factors involving micronutrient molecular structure, pH and bile lipid concentration, and the presence of dietary fat.[37,38] Hydrolysis of the REs is required prior to absorption by the intestinal mucosa, and pancreatic enzymes cholesterol ester hydrolase and pancreatic lipase play an important role in achieving this hydrolysis.[39,40] Dietary fat stimulates pancreatic juice and biliary secretion, which are necessary for lipid digestion and micelle formation providing the necessary lipids to structure the mixed micelles. Higher the percentage of lipid micronutrient incorporated in micelles (known as "bioaccessibility"), higher its absorption efficiency by the intestinal mucosa.[41]

Bioavailability of vitamin A. The bioavailability of vitamin A depends on retinol-binding protein (RBP), retinol: RBP ratio, and RBP: transthyretin ratio.[42] Low retinal concentration can also be associated with systemic inflammation, infections, and macronutrient deficiency due to reduction in plasma carrier proteins, including RBP and prealbumin.[43,44] Interindividual variability of vitamin A in transport, conversion efficacy, or both has been described in literature due to the genetic variations in genes encoding transport proteins for this micronutrient.[45] A varied bio-efficacy due to "low responder" and "high responder" phenotypes should be taken into account for providing an adequate dietary amount of vitamin A. Thus, dietary modifications and assessment of associated systemic conditions are necessary before the administration of exogenous vitamin A supplementation.

Vitamin C (Ascorbic acid)

Vitamin C is one of the important antioxidants in the body protecting from free radicals and reactive oxygen species.[46] Fruits (e.g. Kiwi, strawberry) and vegetables are well-known sources of vitamin C.[47] The beneficial effect of vitamin C in the human eye and the role of high intake of vitamin C in reducing the likelihood of neovascular ARMD had been described in the literature.[48] On the contrary, studies have shown a higher relative risk of exudative macular degeneration with increased vitamin C intake[49] and no significant association between vitamin C intake and prevention of ARMD.[6,34] The recommended daily intake of vitamin C is <1000 mg/day.[35]

Absorption of dietary vitamin C. The majority of intestinal uptake, tissue distribution, and renal reuptake of vitamin C is regulated by sodium-dependent vitamin C transporter (SVCT) family of proteins.[50] Vitamin C absorption takes place across intestinal epithelium *via* membrane transporters either as ascorbate or dehydroascorbic acid (DHA). DHA is either converted to ascorbate inside the cell or transported into the bloodstream *via* glucose transporters. Ascorbate reaches the blood circulation either *via* passive diffusion or facilitated diffusion or some unknown active transporters.[51]

Bioavailability of vitamin C. About 70–90% of vitamin C absorption occurs at dietary intake levels of 30–180 mg/day.[52] At doses above 1 g/day, more than 50% reduction in absorption has been observed with excretion of unabsorbed vitamin C *via* the kidney.[52] Once a plasma concentration of 70–80 μM is achieved, it does not increase further even with increasing dietary intake of vitamin

C.[53,54] From the available literature, a daily intake of about 200–400 mg of vitamin C is adequate in healthy individuals.[55] Polymorphism in SVCTs, smoking, pregnancy, infectious diseases, cancer, cardiovascular disease, stroke, diabetes mellitus, and septicemia affect vitamin C homeostasis and bioavailability.[50] Thus, there is no proven benefit of increased dietary intake of vitamin C.

Vitamin E

It is an essential micronutrient and antioxidant. Vitamin E deficiency could result in lipofuscin accumulation, leading to retinal damage and loss of photoreceptors.[56–58]

A favorable role of vitamin E for preventing the progression of ARMD has been suggested.[59] AREDS2 recommended dosage of 400 IU vitamin E in ARMD.

Absorption of dietary vitamin E. Vitamin E is incorporated in mixed micelles along with lipid digestion products (similar to vitamin A metabolism), which facilitates intestinal absorption. It is dependent on the amount of fat in the meal, which stimulates micelle formation and biliary secretion.[60]

Bioavailability of vitamin E. A multitude of factors affect vitamin E bioavailability. A significant difference in relative absorption rate of vitamin E stereoisomers and between α- and γ-tocopherol has not been observed in humans.[61–63] Dietary fibers are suspected to hamper chylomicron formation by inhibiting lipases and increasing the viscosity of chyme and limiting the diffusion of micelles containing vitamin E to the intestinal brush border. Dietary fibers, however, did not affect vitamin E bioavailability in humans.[64,65] Lipids, however, are considered a major effector of vitamin E metabolism.[60] Genetic factors, including mutation and polymorphism of intestinal proteins involved in vitamin E metabolism, can modulate vitamin E bioavailability. Polymorphism in SCARB1 (scavenger receptor class B type 1), the gene encoding SR-B1 was associated with plasma levels of α- and γ-tocopherol.[66] Besides, health conditions like obstructive jaundice, pancreatitis, and celiac disease affecting enterohepatic circulation affect vitamin E metabolism. Thus, dietary modification and assessment of associated health disorders are important before prescribing vitamin E supplements to enable high bioavailability.

Copper

Copper plays a vital role in the survival of retinal cells.[67] A reduced RPE and choroid complex copper level by 23% was noted in ARMD subjects compared to controls without ARMD.[68] Vegetables, milk, and animal proteins are the common natural sources of copper.

Absorption of exogenous copper. Enterohepatic circulation plays a critical role in copper absorption. Copper absorption has an inverse relationship with the rate of absorption and can fall as low as 12% with a very high quantity of copper intake.[69,70] The reduction in the fraction of copper absorbed at higher dietary intakes is compatible with a carrier-mediated transport process carried out by ceruloplasmin, albumin, and other copper binders.

Bioavailability of exogenous copper. Copper bioavailability from different copper salts has been determined by the slope-ratio technique. With copper bioavailability from acetate salts taken as the reference (100%), bioavailability from sulfate, carbonate, and oxide salts were 88.5%, 54.3%, and 0%, respectively.[71] Studies have hypothesized the role of sodium in increasing the bioavailability of copper by upregulating copper uptake by the intestinal mucosa.[72] Natural vegetable fibers (crude soybean proteins, hemicellulose) have been shown to reduce copper bioavailability.[73,74] Ascorbic acid causes a significant lowering of the bioavailability of copper due to its reduction from cupric to cuprous form.[75] The presence of other organic acids like citric, lactic, and acetic acid, however, contributes to the solubilization of copper and increased bioavailability of the element.[76]

The antagonistic interaction between zinc and copper has been known for decades. Serum and liver copper value reduces linearly as dietary zinc concentration increases.[77] A ternary relation has been noted between zinc, copper, and protein intake where copper deficiency is noted with increased dietary intake of zinc with low protein consumption.[78] Carrier-mediated transportation of copper acts as a rate-limiting factor, and thus, a higher intake of copper is not beneficial.

Omega-3 fatty acids

Alpha linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are the primary omega-3 fatty acids. For maintaining a healthy life, recommended dosage of omega-3

fatty acids ranges from 200 mg/day to 1 g/day.[79] Higher doses of omega-3 fatty acids have been thought to trigger oxidative stress, whereas lower doses exert antioxidant activity.[80] Flaxseed, canola oil, nuts, and oily fish are the main sources of omega-3 fatty acids in the diet.[81]

Absorption of exogenous omega-3 fatty acids. The pathway of metabolism is similar to that of fat-soluble vitamin A. Cholesterol supplementation stimulates absorption by triggering micelle formation and its binding to the intestinal brush border.[82] EPA and DHA are first hydrolyzed into free fatty acids with the help of pancreatic carboxylic acid ester lipase.[81] Factors such as bile secretion, intestinal pH, microorganisms, and fatty acid transport proteins play an integral part in the absorption of these essential fatty acids.[83]

Bioavailability of omega-3 fatty acids. There are varied theories regarding the bioavailability of these essential fatty acids. Phospholipid-bound acids are believed to be absorbed better than triglyceride form due to better accessibility of beta-oxidation pathways.[84] Others believe that the fat content of food is the only decisive factor of rate of absorption and bioavailability.[84] Bioavailability is also influenced by the form in which they exist. A diet rich in ester form of omega-3 fatty acids has lower bioavailability than free fatty acids.[85]

A recommended dosage of omega-3 fatty acids is beneficial for a healthy lifestyle; however, no benefit is obtained from higher doses.

Side effects of antioxidant supplements
1. *Zinc*: High dose of Zinc has been reported to be associated with prostate cancer, memory loss, genitourinary infection, and stress incontinence in women. Excessive absorption of zinc has an inhibitory effect on copper and iron absorption.[86] Zinc toxicity can manifest with nausea, vomiting, loss of appetite, abdominal cramps, gastrointestinal disturbances, and headaches.[87] Misuse of easily available over-the-counter zinc supplements has been reported to cause iatrogenic microcytic hypochromic anemia and leucopenia, not treated by iron supplements. Cupric salts have been used in such cases to treat zinc-associated anemia.[88]
2. *Xanthophyll*: Literature does not mention any short- or long-term toxicity with xanthophyll supplementation.[89,90]
3. *Vitamin A*: Vitamin A intake in higher doses is reported to be associated with abdominal pain, loss of appetite, diminution of vision, lethargy, headache, hypercalcemia, irritability, myalgia, nausea, vomiting, peripheral neuritis, skin desquamation.[91] Beta carotene supplements increase the risk of lung cancer both in smokers and in non-smokers irrespective of the tar or nicotine content of the cigarettes smoked.[92–97]
4. *Vitamin C*: General consensus is that consumption of supplemental vitamin C does not lead to significant adverse health effects. Occasionally, some people might experience diarrhea and gastrointestinal disturbances.[52,98] Formation of calcium oxalate stones due to the enzymatic conversion of ascorbic acid into oxalate in the body has been postulated. Reports on the effect of vitamin C in lithogenesis, however, have yielded contradictory results.[99–104] Individuals with kidney stones should exercise caution before using high doses of vitamin C.
5. *Vitamin E*: Vitamin E supplementation (≥400 IU) is associated with an increased risk of prostate cancer.[105,106] Studies have shown vitamin E could act as a procarcinogenic agent by upregulating bioactivation of carcinogenic enzymes and can promote DNA damage and frequency of cell transformation.[107]
6. *Copper*: Excessive copper intake results in nausea, vomiting, gastrointestinal disturbances, headache, drowsiness, fatigue, diarrhea, and a metallic taste in the mouth, anemia (associated with copper concentrations more than 6 mg/L).[88]
7. *Omega-3 fatty acids*: They are usually not been reported with any severe adverse effects. There is a controversy regarding the association of increased levels of long-chain omega-3 fatty acids in blood with high-grade prostate cancer.[108] This study, however, could not prove fish oil as the cause for prostate cancer, as it is an observational study and not a randomized controlled trial. Contrary to the above-mentioned speculation, Dr. Harris has stated that fish and higher omega-3 fatty acid intake is associated with a lower incidence of prostate cancer and death and a better survival rate among those who already had prostate cancer by delaying the progression of cancer.[109]

Studies highlighting the positive and negative effects of antioxidants have been summarized in Table 2.

It is probably time to rethink the role of antioxidant supplementation in ARMD. Increased prescription and over-the-counter supply of antioxidant formulations have led us to evaluate the risk *versus* benefit ratio of the supplements.

Various questions have been raised from time to time regarding the actual benefit of antioxidants and the stage at which it is more beneficial. AREDS regimen proved to be beneficial only for the group of cases with intermediate ARMD in one eye and advanced ARMD in the other eye. No other groups showed any benefit. AREDS study had a conflict of interest as many investigators had ties to the Bausch + Lomb company (which funded the AREDS study).[119] There are issues of deceptive marketing as well—formulations of some of the top-selling ocular antioxidant supplements in the United States are not identical to those tested in AREDS 1 and 2 trials. Ellingson and Ambati reported in ARVO annual meeting in September 2016 that 73.5% of patients who were taking vitamins did not meet the AREDS guidelines and only 29.6% of the vitamin supplements had a preparation similar to the AREDS formulation.[119]

As an example, Brand X and brand Y are two popular antioxidant supplement brands available in the market at present:
1. Brand X has the following ingredients:
Astaxanthin: 1 mg
Lutein 20%: 5 mg
Zeaxanthin: 1 mg
Vitamin A: 1470 µg
Vitamin C: 50 mg
Vitamin E: 5 mg
Zinc oxide: 40 mg
Cupric oxide: 2 mg
Sodium selenite pentahydrate: 40 µg
PRICE: US$3/pack in India (10 units/pack)
2. Brand Y comprises the following:
Beta carotene: 4800 IU
Elemental Copper: 2 mg
Elemental Manganese: 2 mg
Elemental selenium: 40 µg
Elemental zinc: 10 mg
Lutein: 302 mg
Vitamin C: 40 mg
Vitamin E: 10 IU
PRICE: Rs US$3/pack in India (10 units/pack)

We observed a huge difference in the composition and the dosage of the available supplements, and they also do not seem to adhere to the AREDS 2 formulation given below:
AREDS 2 formulation:

1. 500 mg of vitamin C
2. 400 IU of vitamin E
3. 80 mg of zinc oxide
4. 2 mg of cupric oxide
5. 10 mg of lutein
6. 2 mg of zeaxanthin

Following are some additional points that we would like to highlight regarding antioxidant use:

1. Role of genotype: Independent association of CFH (complement factor H) and LOC387715 genetic variants with progression to advanced stages of ARMD was first reported in 2007 by Seddon and colleagues.[120] A seven times increase in the risk of progression was noted among combined homozygous risk genotypes. Awh and colleagues[121] evaluated the impact of CFH and ARMS2 (age-related maculopathy susceptibility 2) on treatment-specific progression to advanced ARMD. Their results depicted that maximum benefit from zinc-only supplementation could be achieved in patients with no CFH risk alleles and one or two ARMS2 risk alleles. Patients with one or two CFH risk alleles and no ARMS 2 risk alleles had a maximum response from supplementation containing only antioxidants. Treatment with zinc supplement was associated with rapid progression to advanced ARMD in this group. Individuals homozygous for both the risk alleles did not have any benefit from either category of AREDS treatment. Thus, the pharmacogenomic selection of nutritional supplements was postulated in moderate ARMD. Chew and colleagues,[122] however, did not find any significant interaction between supplements and genetics. Another study by Seddon and colleagues[123] published in 2016 noted that subjects with nonrisk genotype for CFH had a significantly lower risk of progression to advanced ARMD after treatment, while those with one or two risk alleles of CFH did not benefit from AREDS treatment.

Table 2. Studies depicting positive and negative outcomes of individual antioxidants in ARMD.

Compounds	Study design	Doses	Outcomes
1. Lutein, zeaxanthin, and meso-zeaxanthin in sunflower oil suspension[110]	Double-blind, placebo-controlled, block-randomized human trial (12 months)	10 mg lutein, 10 mg meso-zeaxanthin, and 2 mg zeaxanthin	*Positive outcomes*: Significantly improved contrast sensitivity of the visual function after 12 months supplementation compared with baseline. Treatment group had significant increase in serum concentrations of the xanthophylls in retina and macular pigment optical density compared with placebo.
2. Anthocyanin supplement[111]	Randomized, parallel study. Postmenopausal, one woman (8 months)	60 mg/day	*Negative outcome* (compared with baseline): No significant increase in macular pigment optical density
3. Vitamin A, vitamin C, and vitamin E[8]	Case-control study		*Positive outcomes*: Low dietary intake of vitamin C and vitamin E was associated with neovascular ARMD. *Negative outcome*: Dietary vitamin A showed no association with neovascular AMD.
4. Vitamin E[112]	Randomized controlled trial (4 years)	500 IU daily	*Negative outcome*: Failed to prevent the development and progression of AMD.
5. Vitamin C and vitamin E[6]	Eye disease case-control study		*Negative outcome*: No statistically significant overall association was found between serum vitamin status and neovascular AMD
6. Vitamins and carotenoids[113]	Prospective observational study		*Positive outcome*: Higher fruit intake related to reduced risk of neovascular ARMD. *Negative outcome*: Vitamins and carotenoid supplements did not have any significant association with ARMD.
7. Vitamins A, C, and E[36]	Prospective population-based study		*Positive outcome*: Strong inverse relation between ARMD and plasma levels of α-tocopherol (vitamin E). *Negative outcome*: No significant association between ARMD and plasma retinol (vitamin A) and ascorbic acid (vitamin C) levels.
8. Vitamins A, C, E, or multivitamins[49]	Prospective cohort study		*Positive outcome*: Vitamin E users had possible but nonsignificant 13% reduced risk of ARMD, while multivitamin users had 10% reduced risk. *Negative outcome*: No reduction in risk for ARMD in vitamin C users.
9. Vitamin E and zinc[58]	Prospective case control study		*Positive outcome*: ARMD patients had lower levels of serum vitamin E and zinc than ARMD-free patients emphasizing the role of zinc and vitamin E in ARMD.
10. Omega-3 fatty acids[114]	Randomized double-blinded placebo-controlled clinical trial		*Positive outcome*: Significant improvement in visual parameters and decrease in drusen cover are were noted in treated early ARMD patients
11. Omega-3 fatty acids[115]	Prospective observational study		*Positive outcome*: Regular consumption of DHA and EPA and fish was associated with significant decreased risk of incident ARMD and may help in primary prevention of ARMD.
12. Zinc and copper[62]	Cross-sectional study (eye tissue from human donors collected at the time of autopsy)		*Positive outcome*: Mean RPE and choroid complex zinc and copper were reduced in ARMD patients compared with ARMD-free patients, suggesting that metal homeostasis plays a role in ARMD and retinal health.

(continued)

Table 2. (continued)

Compounds	Study design	Doses	Outcomes
13. Zinc[116]	Randomized, double-blinded, placebo-controlled study (2 years intervention	Zinc sulfate (200 mg daily)	*Positive outcome*: Significantly increased serum zinc. *Negative outcome*: No significant improvement of eye conditions for patients with AMD.
14. Zinc[9]	Randomized, placebo-controlled clinical trials (followed up for up to 10 years)	Zinc oxide (80 mg daily)	*Positive outcome*: Significantly reduced the risk of developing advanced AMD.
15. Zinc[117]	Prospective, randomized double-masked placebo-controlled study		*Positive outcome*: Vision loss was significantly less in oral zinc–treated group than the placebo group in patients with macular degeneration.
16. Zinc, carotenoids, and vitamins[118]	Retrospective longitudinal cohort study		*Positive outcome*: Zinc supplementation was associated with slow progression of dry form of ARMD (weak association). *Negative outcome*: Zinc intake was unrelated to late ARMD. Carotenoids intake was unrelated to both early and late ARMD.

ARMD: age-related macular degeneration; DHA: dehydroascorbic acid; EPA: eicosapentaenoic acid; RPE: retinal pigment epithelium.

Further genetic studies are required to determine the biological mechanism behind this interaction and its implication to formulate a comprehensive treatment approach for ARMD.

2. The increased financial burden on patients using inappropriate antioxidant supplements.
3. Unawareness among active smokers regarding the risk of lung cancer with beta carotene in the supplements.
4. Side effects of vitamins and antioxidants.
5. A large number of variables affecting the bioavailability of the individual ingredients as discussed above.

Conclusion
Antioxidant supplements have their pros and cons. Perhaps it is advisable to prescribe antioxidant supplementation only to patients who strictly meet the criteria as stated by the AREDS study after weighing the risk *versus* benefit ratio for each individual. Dietary modification should also be discussed for better absorption and bioavailability of the individual vitamins and minerals. Several formulations with variable compositions are available in the market and hence health care professionals should be very careful before advising expensive antioxidants routinely to patients. It may not be prudent to prescribe these formulations without a proper assessment of the individuals' health and dietary status. These supplements should not to be given to patients just for the purpose of providing them with some kind of therapy, as effectiveness of all the components in antioxidant formulations is controversial.

Conflict of interest statement
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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