

The Role of Micronutrition in Age-Related Macular Degeneration

Figen Şermetçi¹, Hakan Özdemir², Levent Karabaş³, Sibel Kadayıfçılar⁴, Süleyman Kaynak⁵

ABSTRACT

Age-related macular degeneration (AMD) is a health problem that can severely impair the quality of life due to irreversible vision loss in the later stage of the disease. While the etiology of AMD involves the presence of unchangeable factors such as genes and age, changeable factors, including diet and smoking, also exist. As the importance of oxidative processes and inflammation has been shown in the pathophysiology of AMD, approaches such as regular use of formulations containing anti-oxidant and anti-inflammatory substances in appropriate doses, diet regulation, and quitting smoking are important for repressing its progression.

Keywords: Age-related macular degeneration, micronutrition, anti-oxidant, resveratrol, omega-3 fatty acids, carotenoids.

Definition and General Information

Age-related macular degeneration (AMD) is an acquired, progressive and degenerative macular disease that affects the photoreceptor complex, retinal pigment epithelium (RPE), and choriocapillaris. It is classified mainly as dry and wet types based on the accompaniment of neovascularization to degeneration. Although there isn't a grading system for AMD that is accepted universally, the Wisconsin Age-Related Maculopathy Rating System uses a simple grading method on standard retina photographs, and the International Age-Related Maculopathy Epidemiology Study suggests a more detailed grading using stereoscopic photographs.^{1,2}

The genetic structure is an important risk factor for AMD. The most important loci are the complement factor H gene on chromosome 1 and the HTRA1/ARMS2 regions on chromosome 10.^{3,4} With age, long been known as a risk factor, the prevalence of the disease increases significantly, especially in individuals of age 75 years or more. Other unchangeable risk factors are listed as female gender, light-colored iris, and skin. Environmental risk factors related to the development of AMD include smoking, ultraviolet exposure, unhealthy diet, hypercholesterolemia, and hypertension.

Epidemiology

Globally, AMD is the third leading cause of blindness after cataracts and glaucoma (8.7%)⁵ and is the main reason of irreversible blindness in aged 60 years and older individuals in developed countries. AMD affects 10% of the population aged 65 and over, and 25% of the population aged 75 and over.⁶ According to one meta-analysis, including studies from Europe, the late AMD prevalence has decreased since 2006. In that meta-analysis, the early and late AMD prevalences were reported to be 3.5% and 0.1% in 55-59-year-olds, and 17.6% and 9.8% in those aged ≥ 85 years, respectively.⁷

Pathophysiology

AMD can be deemed a result of a complex interplay of environmental, genetic, functional, and metabolic factors; nevertheless, the main trigger factor is believed to be oxidative stress.^{8,9} The photoreceptor layer has high metabolic activity. Therefore, it requires a well-functioning nutrition-waste cycle. Oxidative stress causes damage to the RPE which performs these functions.¹⁰ With time, bodies containing lipofuscin and other waste materials cumulatively accumulate in the RPE.¹¹ These accumulated waste materials are pro-inflammatory and can form reactive oxygen molecules.¹² This initiates a vicious cycle.

1- MD, Prof., Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey

2- MD, Prof., Bezmialem Foundation University Faculty of Medicine, Department of Ophthalmology, İstanbul, Turkey

3- MD, Prof., Kocaeli University Faculty of Medicine, Department of Ophthalmology Kocaeli, Turkey

4- MD, Prof., Hacettepe University Adult Hospital, Department of Ophthalmology, Ankara, Turkey

5- MD, Prof., Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Turkey

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Correspondence Address:

Figen Şermetçi

Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Turkey

Phone: +90 312 595 6256

E-mail: fbatioglu@gmail.com

Choriocapillaris gets thinner, and Bruch's membrane degenerates by thickening.¹³ Due to the decreased permeability of Bruch's membrane and other unknown factors, drusen, the tiny yellow or white accumulations of extracellular material, are built between Bruch's membrane and RPE.¹⁴

The formation of drusen indicates dysfunctional RPE, which can lead to loss of RPE and photoreceptor cells.¹⁵ This degeneration of the Bruch's membrane and RPE complex triggers the formation of VEGF and increased VEGF initiates a neovascularization process, namely choroidal neovascularization (CNV), that crosses the Bruch's membrane. These newly formed vessels leak into and under the retina, which ruins the function of the macula and causes hemorrhage. Later fibrosis causes permanent structural changes and loss of function.¹⁶

Risk factors

Age

Although AMD is considered a disease of the population over 50 years of age, early findings can be detected in younger cases. Risk factors significantly related to early AMD include smoking, the occurrence of hearing loss, and a high level of HDL. Among the many risk factors for the development of AMD, the most important factor is age.^{17,18} AMD occurs in 30% of people over the age of 85 in the USA.¹⁹

On the other hand, the prevalence of late AMD was reported to be 1.4% at the age of 70, 5.6% at the age of 80, and 20% at the age of 90.²⁰

Family history and genetics

The prevalence of AMD is the highest in white individuals and the lowest in blacks.

The risk of AMD is 3-6 times higher than the general population in individuals who have first degree relatives with AMD.²¹ In two studies, family history has been shown as an important risk factor for AMD.²²

To date, 52 gene variants have been identified at 34 genetic loci associated with AMD.²³ These genes regulate inflammatory processes, immune response, and the balance of retinal metabolism. The most researched genes among these include the CFH gene on chromosome 1, ARMS gene on chromosome 10, and the CFB/C2 gene on chromosome 6.^{24,25}

Nutrition and lifestyle

Nutrition is found to improve the development of AMD. High consumption of trans fats, saturated fats, and omega-6 fatty acids doubles the prevalence of AMD, while nutrition

with unsaturated fats is protective against AMD.²⁶

The Eye Risk Consortium's study, which combined the findings of Rotterdam and ALIENOR studies, showed that higher Mediterranean diet adherence reduced the risk of the incidence of late AMD as 41%.²⁷

In a case-control study conducted at Hacettepe University Department of Ophthalmology, high dietary intake of carotenoids, vitamin C, vitamin E, zinc, and omega 3 was found to decrease the risk of development of AMD. On the other hand, smoking, advanced age, high consumption of red meat, and omega-6 increase this risk.²⁸

Smoking

Smoking is the most significant preventable risk factor. The risk of AMD is 2-4 times higher in individuals who have a long history of smoking compared with non-smokers of the same age. Therefore, individuals showing early AMD symptoms and/or family history should be encouraged to quit smoking.^{18,29} Smoking is hypothesized to affect the development of AMD via mechanisms that increase oxidative damage, trigger neovascularization, disrupt the choroidal blood flow, and stimulate the immune system, including the complement pathway.³⁰⁻³²

Other risk factors

The data obtained from two large population-based cohort studies, namely Beaver Dam and the Blue Mountains Eye Studies, indicated that older individuals who have had cataract surgery have a greater risk of developing late neovascular AMD.³³

In a systematic meta-analysis, including six case-control studies and eighteen cross-sectional and prospective studies involving 113,780 people, the strong risk factors were advanced age (60 years and older) family history of AMD, previous cataract surgery, and smoking. Additionally, moderate risk factors included high plasma fibrinogen, high body mass index, hypertension, and cardiovascular disease.¹⁸

Classification and Staging

AMD is traditionally considered to be of two main forms, dry and wet; nevertheless, there is no agreement on specific definitions. The dry form (non-exudative) constitutes about 90% of patients. Geographic atrophy (GA) is considered the late stage of the dry form of AMD. The wet type (exudative) is associated with faster progression to vision loss, although it is less common than the dry form. The main symptoms of the wet form of AMD are pigment epithelial detachment (PED) and CNV. Nearly 10-20% of non-exudative AMD cases may turn into the wet type.³⁹

The Age-Related Eye Disease Study (AREDS) defined the stages of AMD according to the characteristics of drusen, atrophy, and neovascularization (Table 1).³⁴

Clinic and Diagnosis

AMD patients are admitted to the hospital with complaints of decreased visual acuity, loss of central visual field, distorted vision, and/or difficulty in daily activities such as reading, watching television, and face recognition. Metamorphopsia is a key clinical symptom of macular diseases, including AMD.^{35,36} AMD is primarily characterized by drusen and pigment epithelial changes in the early and intermediate stages. Findings are generally symmetrical between two eyes, but the type, number, size, distribution of drusen varies from person to person.³⁷ Pigment disorders such as local hyperpigmentation or hypopigmentation are a common finding in AMD. Well-demarcated, progressive atrophies of the RPE can be seen in the perifoveal region. These atrophic areas can enlarge and merge to form geographic atrophy (GA).³⁸

Wet type AMD can emerge with PED, intraretinal hemorrhages and CNV.³⁹ Main diagnostic methods are fluorescein angiography, fundus photography, and optical coherence tomography (OCT).⁴⁰ We can add indocyanine green angiography, fundus autofluorescence (FAF), and OCT angiography which has come to use in recent years. FAF imaging is dependent on stimulated light emission from molecules, mainly lipofuscin, in the RPE. This imaging is a useful method to assess and monitor the topographic structure and RPE health since localized lipofuscin accumulation in RPE cells causes increased autofluorescence. On the other hand, decreased or absent lipofuscin in the RPE will result in decreased FAF signaling.^{41,42}

Prophylaxis and Treatment

Currently, there isn't any approved treatment for dry AMD. Various treatment studies are carried out for inflammation and genetic polymorphisms.⁴³ There are also no accepted methods for the management of advanced dry AMD other

than monitoring the development of CNV and changes in the area of GA and using visual rehabilitation tools when necessary.⁴⁴ It is important to self-test with an Amsler card for detecting early changes although the sensitivity of the test is low.⁴⁵

The aging of the population and the corresponding increase in the number of patients with AMD significantly increase the social and economic burden on both families and societies.⁴⁶ Therefore, great efforts have been made to reduce the progression of the disease.

The effects of anti-oxidant macular carotenoids, vitamins, and minerals are significantly understood. Epidemiological data have shown that wet AMD development risk is lower in patients with high serum anti-oxidant concentrations. It has been shown in large prospective epidemiological studies that the use of lutein and zeaxanthin reduces AMD risk in the long term.^{47,48} Previous epidemiological studies showed that various factors such as inflammation, increased light exposure, and oxidative stress have a strong relationship with AMD; however, subsequent studies have led to no definite conclusion.⁴⁹⁻⁵²

The Age-Related Eye Disease Study (AREDS)

It is a randomized, double-blind, multicenter clinical trial initiated by the American National Eye Institute in 1990, involving 3640 people from 11 centers.⁵³ In the study it is aimed to investigate the effect of zinc and other anti-oxidant vitamins above the daily recommended doses on AMD progression in the elderly. In this epidemiological study, cases with diffuse small drusen, medium or large drusen, CA, or pigment abnormalities in one or two eyes and vision loss because of advanced AMD in one eye were included. Cases were randomized to one of the four treatment groups: 1) Anti-oxidants (400 IU vitamin E, 500 mg vitamin C, 15 mg beta-carotene), 2) Zinc (80 mg zinc oxide and 2 mg copper oxide), 3) Anti-oxidants plus zinc, and 4) placebo. The formulation of AREDS was chosen based on the recommendations of an expert committee. Lutein and zeaxanthin were not commercially available at the time

No AMD	No drusen or bilateral few small drusen (<63 µm), with normal dark adaptation
Early AMD	Widespread small drusen or medium-sized drusen fewer than 20 (between 63-125 µm) or pigment anomalies, impaired dark adaptation
Intermediate AMD	At least one large drusen (>125 µm), widespread intermediate drusen, non-central geographic atrophy, pigment anomalies
Late AMD	Visual acuity less than 20/32 because of central geographic atrophy and/or choroidal neovascularization (subretinal hemorrhage, RPE detachment, fibrovascular scar, lipid exudates)

of the study; therefore, beta carotene [15 mg (25,000 IU/day)], with well-documented anti-oxidant properties, was included in the formulation, although it is found in trace amounts in the retina. Daily 2 mg copper oxide was added to prevent anemia due to a high level of serum zinc. In this study, the estimated possibility of progression to advanced AMD at the end of 5 years was found to be 28% in the placebo group, 20% in the anti-oxidant plus zinc group, 23% in the anti-oxidant group, and 22% in the zinc group. The risk of AMD in the anti-oxidant plus zinc group was significantly decreased when compared with the placebo group (99% CI: 0.52-0.98, OR: 0.72).

After these results were published in 2001, there have been developments in the use of nutritional supplements for AMD, and this led to the initiation of the AREDS2 clinical trial.⁵⁴ Besides, new evidence has emerged during the AREDS trial about the fact that lung cancer risk in smokers increases with β -carotene supplementation.^{55,56} Almost 50% of the USA population are former or active smokers and are at risk for AMD; this finding raises concerns about β -carotene.

AREDS2

The AREDS formulation was released in 2001 after the completion of the study. This formulation, with certain modifications, has been used by individuals who are at risk of vision loss because of AMD. In 2006, AREDS2 was initiated to evaluate the effect of using lutein and zeaxanthin instead of beta carotene in AREDS formula and adding omega-3 long-chain polyunsaturated fatty acids (PUFAs) to the formula. A subgroup, in which a lower amount of zinc (35 mg) was given, was formed because evidently, a larger amount of zinc cannot be absorbed, and a high level of zinc can create problems related to the genitourinary system.^{57,58} Active and ex-smokers are randomized to subgroups not including β -carotene. When groups receiving lutein and zeaxanthin and no β -carotene were compared with groups receiving β -carotene but no lutein and zeaxanthin in subgroup analysis, lutein-zeaxanthin was found to be more effective, especially in preventing the development of wet advanced AMD ($p < 0.05$).⁵⁹

However, AREDS2 failed to meet the ambitious target of being 25% more efficient than the AREDS formulation but was found to be an effective and especially reliable option in smokers.^{59,60}

Unlike other studies, neither benefit nor harm was demonstrated for AMD with omega-3 fatty acid supplementation in AREDS2.⁵⁹

In the updated formulation with AREDS2 recommendation, lutein/zeaxanthin replaced the beta-carotene. Com-

ponents and daily doses based on AREDS2 results are suggested as follows: 80 mg zinc, 2 mg copper, 500 mg vitamin C, 400 IU vitamin E, 2 mg zeaxanthin, and 10 mg lutein. Macular pigment density was not assessed both in AREDS and AREDS2 because that analysis is time-wasting.

Macular Pigments and AMD

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Green leafy vegetables (parsley, spinach, cabbage, lettuce, zucchini, broccoli, etc.), orange-yellow fruits (orange, mango, papaya, and tangerine) are important macular carotenoid sources.^{61,62}

In food sources, most common macular carotenoid is lutein. Zeaxanthin is present in smaller amounts. On the other hand, meso-zeaxanthin is rarely found in human diet and is synthesized in the body from lutein.⁶³ Shyam et al. found that RPE65 protein is responsible for the transformation of lutein to meso-zeaxanthin in the RPE of vertebrates.⁶⁴

Macular pigments (MP) can be found in high concentrations at the fovea, inner plexiform layer, and Henle's layer.⁶⁶ The highest concentration of MP is in Henle's layer, at about 0.1 to 1 mM, and the concentration decreases rapidly away from the center.⁶⁷ The lutein-zeaxanthin ratio is 1/2.4 (0-0.25 mm) in the center, while it is more than 2/1 at the periphery (8.7-12.2 mm). MP concentration in the peripheral retina was estimated to be one percent of the fovea. This alteration was directly related to the alteration in the rod/cone ratio.⁶⁷ The level of MP varies greatly between individuals. In healthy individuals, the optical density of the macular pigment decreases significantly with age.⁶⁸

Lutein and its isomers are located both perpendicular and parallel to the plane of biological membranes, while zeaxanthins are located perpendicularly.⁶⁹ The transmembrane localization of lutein and zeaxanthin reduce the susceptibility of the membrane to lipid oxidation and increases the stiffness of the lipid bilayer, and hence functions as a "molecular rivet".⁷⁰

The main function of the MP is reducing blue light scattering in the central retina. The anatomical location and dark yellow color of the MP are deemed favorable for protecting foveal region against photooxidative damage. All MP molecules reduce blue light exposure of photoreceptors and RPE, but lutein filters blue light more effectively than zeaxanthin and meso-zeaxanthin owing to its orientation in the lipid layer.⁶⁹ Chucair et al. showed that retinal neurons of rats are more effectively protected against oxidative stress when treated with macular carotenoids compared with those in the untreated group.⁷¹ Primates that fed a xan-

thophyll-free diet since birth were found to be more prone to damage caused by blue light.⁷²

The transport of carotenoids to relevant target sites is mainly performed by LDL, HDL, VLDL, albumin, and chylomicrons, and their receptors, namely CD36 and SRB1, while hydrophobic carotenes as lycopene and beta carotene are transported with LDL, and hydrophilic carotenes as zeaxanthin and lutein are transported with HDL.^{73,74}

Likewise, the transport of macular carotenoids from serum to the retina is performed mainly by retinoid transporters as retinol-binding protein 4 (RBP4) and tubulin interphotoreceptor retinoid-binding protein (IRBP).^{75,76}

Data from double-blind, placebo-controlled, randomized studies show that there exists a relationship between the increase in the MP optical density and visual function improvement. This may be because of short wavelength filtering of MP that improve the contrast sensitivity by reducing the flare, light scattering, and chromatic aberration.⁷⁷

The greatest improvement in visual function is observed in persons with the lowest basal MP concentration.⁷⁸ Therefore, in both healthy and diseased retinas, MP appear to have a beneficial role, although a crystalline maculopathy may develop at overdose.⁷⁹ Visual acuity usually does not increase with an increase in MP density, although improvements in contrast sensitivity, reductions in glare, and an increase in average reading speed are frequently observed.⁸⁰

Individuals, who use computers or smart phones for more than six hours a day, benefit from carotenoid supplementation in terms of increased sleep quality and visual performance, and decreased visual fatigue and photophobia.^{81,82} As a result, macular pigment support is beneficial even when there is no occurrence of AMD.

In individuals that have early or intermediate AMD, 24 single-nucleotide polymorphisms (SNPs) have been reported in 5 genes related to the transport and metabolism of zeaxanthin and lutein.⁸³ This finding supports the protective role of macular carotenoids against AMD. These genetic variations might also explain the absence of protective effect of zeaxanthin and lutein in AMD patients in certain epidemiological studies.^{84,85}

High consumption of zeaxanthin and lutein in diet decreases the prevalence of AMD.^{85,86} Özyurt et al., determined in their study that the serum levels of zeaxanthin and lutein were lower in wet AMD cases when compared with the control group.⁸⁷

Lutein and zeaxanthin are overall safe to supplement at the recommended doses for human consumption; The European Food Safety Authority (EFSA) has set this value for lutein at 1 mg per kilogram.

Omega-3 Fatty Acids

Omega-3 fatty acids are long-chain fatty acids containing more than one double bond. They suppress the inflammation due to omega-6 fatty acids, like arachidonic acid. Several preclinical and epidemiological studies have shown the beneficial effect of omega-3 fatty acids on degenerative diseases like AMD in which inflammation has a role in pathophysiology.⁸⁸⁻⁹² Nowadays, the Omega-6/Omega-3 ratio, which should be 2/1 in a healthy diet, is estimated to increase to 25/1 level due to dietary habits. The recommended daily intake of DHA and EPA in the diet is between 250 and 1000 mg in total.⁹³ The photoreceptor membranes contain a large amount of DHA that is important in maintaining retinal functions, photoreceptor differentiation, and survival.⁹¹ In AREDS2, DHA, and EPA (350 mg+650 mg) were added to the AREDS formulation, and the effects were compared with those in other groups (placebo, L+Z, L+Z+Omega-3). In this population, omega-3 fatty acids did not significantly contribute to reducing the risk of progression to late AMD against all odds.⁶⁰ However, in the secondary analysis, omega-3 fatty acids were found to reduce the progression to geographic atrophy from bilateral drusen (95% CI 0.23-0.87, OR 0.44).⁹⁴

Anti-oxidant Vitamins and Minerals

Natural anti-oxidants can be defined as critical molecules in maintaining optimum health in animals and humans and can prevent cellular damage against free radicals.⁹⁵ Epidemiological studies support the possibility of decreased progression of AMD as a result of increased uptake of anti-oxidants, especially carotenoids, vitamin E, and C with diet.⁹⁶

Vitamin C

Vitamin C (ascorbic acid) is deemed necessary for protection against disease processes caused by oxidative stress. It is the most effective anti-oxidant in human blood.^{97,98} while a low level of plasma vitamin C has been associated with increased AMD risk, high concentrations are not protective.⁹⁹

Vitamin E

The fat-soluble tocopherol compounds are mainly available in eight different forms. A dose of 1 IU of synthetic vitamin E corresponds to 0.66 mg. The recommended daily dietary

intake is 22 IU (15 mg). In the AREDS and AREDS2 formulations, 400 IU vitamin E was used. In the Rotterdam Study, which is a population-based cohort consisting of participants aged ≥ 55 , a negative relationship between dietary intake of vitamin E and AMD was observed after eight years of follow-up.⁹⁷ The tolerable upper intake level of synthetic vitamin E was accepted as 1100 IU. Higher doses can cause bleeding diathesis, especially in individuals using anticoagulants and antiaggregants.

Vitamin D

Besides being the regulator of calcium metabolism in the body, vitamin D has potent anti-inflammatory and anti-angiogenic effects. Thus, it may have a preventive role in AMD because of its effects on these mechanisms, which are also involved in the pathophysiology of AMD. Vitamin D shows its anti-inflammatory effects via the suppression of pro-inflammatory cytokines such as tumor necrosis factor- α and interleukin (IL)-2 and increasing the release of cytokines that inhibit inflammation such as IL-4, IL-10, and transforming growth factor- β .

The possible protective effect of vitamin D against AMD was first reported by the National Health and Nutrition Examination Survey (NHANES) study in 2007.¹⁰⁰ Although the relationship between vitamin D and AMD is controversial, most of the studies and meta-analyses support the positive effect of vitamin D.¹⁰¹ In a study on postmenopausal women (under 75 years old), an inverse relationship was observed between a high level of serum vitamin D and development of early AMD.¹⁰² High serum levels reduce the development of early AMD and reduce the development of advanced AMD by 40%.^{103,104} In a study investigating the effect of vitamin D-related genes and vitamin D serum level on the development of AMD, a relation between serum levels under 30 nm/L and neovascular AMD was observed.¹⁰⁵ Kan et al. compared vitamin D serum levels between AMD patients and the control group and found a significantly low vitamin D serum level in AMD patients.¹⁰⁶ In one meta-analysis, a high vitamin D serum level was reported to be related to a low prevalence of AMD.¹⁰¹ In another meta-analysis, high serum levels do not reduce the risk of AMD development. On the other hand, a serum level below 50 nmol/L was found to be related to advanced AMD.¹⁰⁷

All the evidence shows that vitamin D is effective in the development of AMD, although it is difficult to show its solitary effect in a multifactorial disease such as AMD. Similarly, single vitamin intake did not have an important effect on the prevention of AMD, but the risk of AMD could be reduced with the combined intake of antioxidants and vitamins.¹⁰⁸

Zinc

Zinc is second most abundant trace metal in the human retina after iron. Zinc deficiency can cause worsening of dark adaptation and reduced photopic and scotopic responses.^{99,109} Zinc is the cofactor of various metabolically active enzymes in the eye, including catalase and superoxide dismutase, that are substantial in retina protection from oxidative damage. It also suppresses the chronic inflammation at the border of RPE/choroid and reduces neovascular AMD risk.¹¹⁰ The amount of zinc is decreased at neuroretina and RPE with age, and this reduction is related to AMD.¹⁰⁹ In Rotterdam and BMES studies, zinc intake was found to be related to a reduced risk of both early and late AMD. Additionally, the Beaver Dam Eye Study reported a reduced risk of early AMD due to zinc intake.^{97,111,112} The recommended dose of 80 mg in AREDS is a high dose that can cause gastrointestinal, urological, and hematological side effects; therefore, lower doses are used in current formulations.

Other elements

Copper is an essential trace element that has important roles in the oxidoreduction and scavenging of free radicals.¹¹³ Selenium is an essential component of protein-containing selenocysteine and plays a significant role in sustaining the redox state of the cell and scavenging reactive oxygen species. The anti-oxidant activity of selenium is associated with glutathione peroxidase.¹¹⁴ However, there is no evidence of the beneficial effect of selenium and copper supplementation in AMD.

Resveratrol

Resveratrol is a natural polyphenol found in plants. Fruits of the *Vaccinium* species such as red wine, grapes, grape juice, cocoa, peanuts, raspberries, mulberry bark, cranberries, and blueberries are particularly rich resveratrol sources. Even though red wine is a relatively rich resveratrol source, other polyphenols are found in higher concentrations than resveratrol in red wine. The resveratrol presents two isomers, cis and trans. The dominant form of resveratrol in grape juice and grapes is the trans form, however many wines contain important amounts of cis-resveratrol as well.¹¹⁵

In vitro tests revealed that resveratrol prevents sodium iodate-induced apoptosis of human RPE cells and oxidative stress.¹¹⁶ It has been shown that resveratrol protects RPE cells against acrolein-induced cytotoxicity via increasing the mitochondrial bioenergetics.¹¹⁷

Resveratrol also protects the RPE cells against the in vitro apoptosis induced by autoimmune antibodies, which is very important in autoimmune retinopathies.¹¹⁸ It has a

protective effect against light-induced retinal degeneration by reversing retinal activating protein-1 (AP-1) activation, which regulates apoptosis and inhibits the increased SIRT1 activation due to light exposure.¹¹⁹ The c-fos expression was reduced in retinal extracts of resveratrol treated mice, which in turn inhibited the death of photoreceptor cells by suppressing AP-1 activation. This anti-apoptotic effect can significantly contribute to the prevention of a neurodegenerative disease such as AMD.¹¹⁹

Resveratrol exhibits a dose-dependent protective effect against hydrogen peroxide induced cytotoxicity in human retinal RPE cells via increasing the activities of enzymes such as catalase, glutathione peroxidase, and superoxide dismutase that are responsible for the inhibition of intracellular levels of ROS. Although the number of studies is limited, they emphasize the significance of reducing oxidation amount that occurs in the retina of patients with AMD and suggest that supplementation of resveratrol can be beneficial in preventing oxidative stress induced-RPE degeneration in these patients.¹²⁰

The anti-inflammatory and anti-oxidant characteristics of resveratrol decrease the prevalence of CNV. Nagineni et al. showed that the resveratrol added to human RPE cell culture suppresses the secretion of vascular endothelial growth factor (VEGF)-A and VEGF-C induced by hypoxia and inflammatory cytokines.¹²¹ Resveratrol inhibits the secretion of VEGF-A by reducing the hypoxia-induced factor (HIF)-1 α transcription factors and deacetylation.¹²²

The resveratrol-based nutritional supplement was used in three patients aged 80 years with wet AMD who refused anti-VEGF therapy. In these cases, the retinal structure was observed to be anatomically restored, RPE function and choroidal blood flow were improved, visual acuity increased, and these effects lasted up to three years.¹²³

Other Materials

It has been shown in experimental studies that cadmium and lead accumulate in human ocular tissues, especially in the choroid and RPE.¹²⁴

Cadmium content in retinal tissue in humans increases because of age and smoking. A higher level of cadmium was detected at RPE and neural retina in AMD patients when compared with that in control patients.^{125,126}

Melatonin scavenges the hydroxyl radicals and protects the RPE against oxidative damage. The physiological decrease in melatonin in elderly patients might be a significant factor in the dysfunction of RPE. It has been shown in clinical studies that daily intake of 3 mg melatonin protects the retina and delays the macular degeneration.¹²⁷⁻¹²⁹

Conclusion

The retina is one of the most at-risk organs in terms of oxidative stress because of its high metabolic activity. AMD occurs as a result of the cumulative effect of oxidative stress, environmental factors, and metabolic waste materials. The balance between the factors preventing and facilitating AMD development should be in favor of preventive factors. AMD patients should especially reduce lifestyle-related modifiable risk factors. These measures for reducing the risk factors include; quitting smoking,¹³⁰⁻¹³³ intake of a healthy and balanced diet rich in nutrients such as vegetables, fruits (natural anti-oxidants), and fatty fish (the main source of omega-3 PUFAs like EPA and docosahexaenoic acid [DHA]).¹³⁴⁻¹³⁹ Efforts should be made to control other systemic factors such as hypertension, hyperlipidemia, atherosclerosis, and obesity.¹⁴⁰ Although the genetic structure does not affect the response to micronutrition, and genetic testing may be recommended for risk assessment in patients that have a family history for AMD.¹⁴¹

Studies have shown the beneficial effect of treatment with anti-oxidants (i.e., vitamin C, vitamin E, zeaxanthin, lutein, copper, zinc) in intermediate AMD. AREDS showed that the development of advanced AMD is statistically significantly reduced with the intake of anti-oxidants (namely beta-carotene, vitamin E, vitamin C) and zinc. AREDS2 goes a step further and adds macular pigments like zeaxanthin and lutein, and omega-3 fatty acids into the formulation. Resveratrol is added to various products since later studies have supported its positive effects. Micronutrition is not a one-size-fits-all suit. For each patient, an appropriate choice should be made after evaluating the AMD type, stage, family history, habits, general health status, and medications used. Patients should be warned about not consuming random micronutrient supplementation. Taking all possible preventive measures should be an important necessity in the fight against this disease, which seriously affects the quality of life in a significant part of society.

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