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AGE-RELATED MACULAR DEGENERATION (AMD), SUPPLEMENTS AND NUTRITION - WHAT DOES THE EVIDENCE TELL US?

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review paper

Summary

Age-related macular degeneration (AMD) is a disease of the macular area and is the most common cause of irreversible vision loss in people over 50 years of age. Many AMD risk factors, including aging, smoking, exposure to UV and blue light, chronic inflammation, and improper diet, can be associated with oxidative stress. In this regard, certain food ingredients and supplements that have antioxidant properties may contribute to the prevention of AMD and it's progression. Polyphenols can be considered as preventive and therapeutic compounds in the prevention of diseases associated with aging due to the antioxidant properties. For example, quercetin, present in onions, improves anti-VEGF therapy, which is the only effective drug for the wet form of AMD, while resveratrol, found in grape skin, red wine, blueberries and mulberries, neutralizes the negative effects of anti-VEGF therapy. Blueberry anthocyanins have a protective effect on induced damage of retina caused by blue light. Carotenoids that are part of the macular pigment; lutein and zeaxanthin, found in leafy green vegetables and eggs, have the ability to filter light ("natural sunglasses"), but also have direct antioxidant properties. Zinc and copper homeostasis in the retina-choroid complex also play a role in retinal health and AMD prevention. Adequate intake of omega-3 fatty acids, which are found in blue fish, nuts and seeds, reduces the risk of progression to the late stage of AMD. Oxidative stress can be exacerbated by improper diet, and thus increase the possibility of the occurrence and progression of AMD, which is why during the eye examination of persons at risk, it is necessary to advise on proper nutrition and appropriate supplementation.

Keywords: Age-related macular degeneration (AMD), oxidative stress, antioxidants, supplements, nutrition

Introduction

Age-related macular degeneration (AMD) is a medical condition of macula and is the most common cause of vision loss in persons over 50 years of age.
There are two types of age-related macular degeneration: dry and wet form.
Dry macular degeneration or "early" stage of AMD is characterized with presence of yellow deposits (called drusen) in macula, hypo/hyperpigmentation of retinal pigment epithelium, which is often found in macula and posterior pole. Wet form of macular degeneration or "late" stage of AMD is more serious condition and includes occurrence of choroidal neovascularization (CNV), retinal and subretinal bleeding, subretinal exudates, periretinal and retinal fibro-glial changes, geographic atrophy in RPE as well as pigment epithelial detachment (PED). Unless treated, wet form of macular degeneration can lead to dramatic decrease of visual acuity within a year (Andrijević Derk, 2015).
Besides classic categorization on dry and wet macular degeneration, there are more detailed classifications. The classification of dry form of AMD relates to number and size of drusen and the changes in RPE. We discern, early stage (Fig. 1a) with soft drusen, 64-124 μm in size and light pigment changes on the posterior pole, and intermediate stage (Fig. 1b) with middle-sized drusen resulting in confluence and big drusen (> 125 μm) accumulated below retina. Late stage of ADM has two subtypes: wet, exudative or neovascular macular degeneration (Fig. 1c) and geographic atrophy or dry degeneration (Fig. 1d) (Žorić et al., 2008).
According to the literature, a dry form of AMD present in 10 - 20 % of patients progresses to wet form, where 40% of patients develop wet form of AMD on both eyes (Andrijević Derk, 2015).
The data from EUREYE study (2006) shows that 3.3% of the population over 65 years have some form of AMD on at least one eye (Andrijević Derk, 2015). It is believed that in Europe by 2040, the number of people with early AMD will be between 14.9 and 21.5 million and those with late AMD between 3.9 and 4.8 million (Colijn et al., 2017).
AMD is the leading cause of blindness in developed world and among white population of USA and constitutes 9% of blindness on global level. It is estimated that in 2020, number of people suffering from AMD will be 196 million globally and in 2040 that number will increase to 288 million (Chew, 2020). The World Health Organization states that

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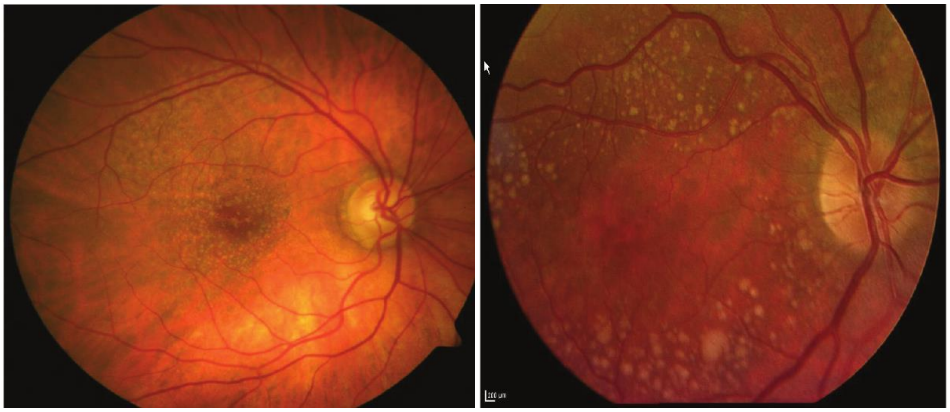
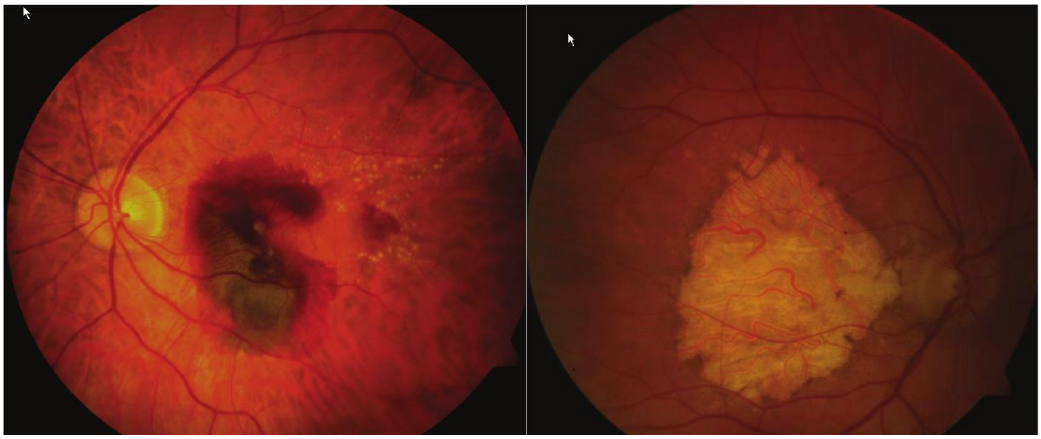
currently there are 14 million people suffering from blindness or heavily damaged vision due to AMD which puts it as a major problem related to vision loss on a global level (Pawlowska et al., 2019).



a) Early stage of AMD b) Intermediate stage of AMD



c) Late stage with neovascularization d) Late stage with geographic atrophy

Fig. 1. AMD stages (Čeklić et al., 2015)

AMD risk factors and pathogenesis

The main factor of AMD occurrence is age-related (50 years and above), then positive family history, smoking, previous operation of cataract, atherosclerosis, obesity followed by increased Body Mass Index (BMI), artery hypertension and cardiovascular diseases, insufficient intake of vitamin A, C and E, omega-3 fatty acids, zinc and lutein in diet, genetic predispositions (polymorphism related to complement H, ARMS2/HTRA1). Possible risk factors are: alcoholism, sun and UV exposure, intake of vitamin B, hormonal status and quantity of vitamin D, C reactive proteins and markers of inflammation (Čeklić et al., 2015).

Smoking as a risk factor is connected with specific genetic factors. High levels of cadmium in urine, occurring in smokers suffering from maculopathy, indicates specificity in its elimination in this group. Smokers who do not suffer from maculopathy have significantly lower levels of this toxic metal (Erie et al., 2007).

The mutation of the complement factor H (CFH) is probably the most noticeable genetic change in patients suffering from AMD (Warwick et al., 2018). Variability of several loci not included in the complement system plays an important role in AMD pathogenesis. Those are ARMS2 gene (Age-Related Maculopathy Sensitivity 2 gene) on chromosome 10 and genes included in angiogenesis (TGFBR1, VEGFA), the high-density cholesterol pathway -HDL (APOE, CETP i LIPC) and immunity regulation (PILRB) (Toomey et al., 2018). Epigenetic regulation of gene expression should also be included in the studies related to AMD pathogenesis, but epigenetic mechanisms in AMD early development are less known than genetic mechanisms. White people and females are most commonly connected to this disease.

However, besides age, family medical history, genetic predisposition and smoking, other risk factors are still controversial and require further examination

in order to confirm their participation in AMD pathogenesis (Pawlowska et al., 2019).

AMD is multifactorial disease which is mainly caused by the changes in RPE structure and metabolism as a consequence to changes in Bruch's membrane (BM) caused by aging of the organism. All of these changes start with the fourth decade of life and are expressed more with age, and the result is change in RPE metabolic activity. BM in macula is more affected with metabolic changes than peripheral BM due to higher density of photoreceptors in macula and RPE metabolic activity. Metabolic activity of RPE involves a complex process of removing products of photoreceptors activity (rods and cones), which are at the same time regenerating, removing damaged membrane parts and organelle cytoplasm which due to change in transport through Bruch's membrane, are accumulated in the form of basal laminar deposit (BlamD) and basal linear deposit (BlinD), drusiform changes (D) in the area of cytoplasm of RPE and basal membrane of RPE and Bruch's membrane. Changes within collagenous and elastic layer of Bruch's membrane lead to mineralization of elastic layer as well as thickening of membrane from 2 μm during the first ten years of life up to 4.7 μm in the nineth decade of life. Moore's and Clover's study shows tenfold decrease in transport through Bruch's membrane between the first and ninth decade of life, with all of the changes being more expressed in macular area in comparison to periphery (Andrijević Derk, 2015).

It is generally accepted that oxidative stress plays an importantrole in pathogenesis of AMD, but the source of oxidative stress in AMD is not generally known. AMD, especially wet form, is linked to several changes in retinal vascularization, which can be attributed to aging or intensive flow of blood in this tissue. These changes along with genetic predisposition of an individual, environmental factors and lifestyle represent major pathogens of AMD (Pawlowskaet al., 2019).

Retina is exposed to sun radiation during the lifetime. It is considered that the blue part of solar spectrum has more significant impact here because cornea and lens absorb the most part of UV radiation (Žorić et al., 2008). Retina has the highest speed of metabolism among tissues in the human body, has a large need for oxygen and is highly susceptible to oxidative stress (Datta et al., 2017). Oxidative stress is the condition leading to disbalance between antioxidants and prooxidants, in favor of prooxidants. In the balanced conditions, free radicals are dissolved by antioxidants of the cells with the help of enzymes (superoxide dismutase, catalase, glutathione peroxidase) or nonenzymatic with the help of glutathione. Long term oxidative stress leads to the damage of biological macromolecules (DNA, lipids, proteins and carbohydrates) causing disbalance of homeostasis in the cell and later in the tissue (Brzović Šarić, 2014). Oxidative damage of lipids - lipid peroxidation has the major role in AMD pathogenesis. Photoreceptor membranes contain a lot of polyunsaturated fatty acids (PUFA), a source of reactive oxygen species (ROS). Chronical exposure to light results in the ROS production. The cells of retinal pigment epithelium are of crucial significance for phototransduction because they phagocyte old tips of photoreceptors outer segments (Sun et al., 2006). Lipofuscin comes as a byproduct of phagocytosis (Delori et al., 2001). Lipofuscin contains complex compound of bis retinoid fluorophore which are causing autofluorescence of the fundus of the eye (Sparrow et al., 2012). The main fluorophore is A2E (N-retinylidene-N-retinylethanolamine), pyridiniumbisretinoid. When A2E is exposed to blue light, it succumbs to photooxidation which results in the ROS production and lipid peroxidation. Oxidative processes in retina, especially those happening during aging of macula can contribute to AMD pathogenesis. Aging, main risk factor of AMD occurrence, is related to ROS over-production in different ways, including lower levels of antioxidants, antioxidative enzymes and accumulation of damages on mitochondrial DNA (mtDNA). Macula concentrates light and shows high metabolic activity and oxygen consumption related to intensive flow of blood. Retina has limited regeneration mechanism and does not possess stem cells which could produce new cells to replace dead ones.

Environmental factors and lifestyle, including exposure to blue light, smoking, and improper diet increase ROS production. However, some nutritive supplements can inhibit oxidative stress related to ROS over-production and alleviate retinal damage. Retinal antioxidant defense can directly inhibit oxidative stress and its byproducts including lipid peroxidation, but is decreasing with age; limited regeneration mechanisms and regeneration of retina also decreases with age, as shown in fig. 2 **(**Pawlowska et al., 2017).

Many factors that can increase the risk of AMD, including smoking, exposure to UV and blue light, chronic infections and improper diet, could be related to oxidative stress, but it is not known if oxidative stress is a part of occurrence or consequence of the disease or both. In any case, reduction of stress can be extremely important in the prevention and therapy of AMD.

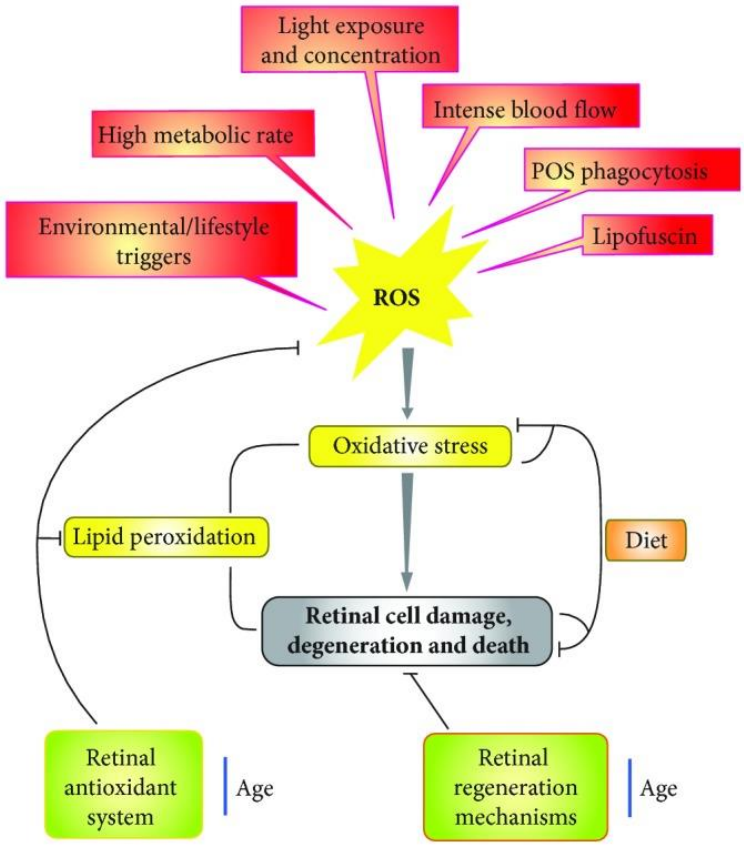


Fig. 2. Risk factors, oxidative stress and the impact of retinal damage in pathogenesis of AMD with representation of defense mechanism; influence of proper diet, retinal antioxidative system and retinal regeneration mechanisms, which decrease with age (Pawlowska et al., 2019)

Antioxidants in retina

Retina has more elements of antioxidant defense; vitamin C and E, carotenoid, lutein and zeaxathin are often considered the most important (Carneiro et al., 2017).

Vitamin C and E are well-known antioxidants.

Both vitamins contribute to the reduction of retinal epoxy adduct as well as the prevention of damages caused by blue light (Sparrow et al., 2003).

Vitam E or α-tocopherol can prevent chain reaction of ROS during the attack on the cell membranes. In order to stabilize ROS, α-tocopherol is turned to α-tocopherol radical which has stable and not reactive form. α-tocopherol radical can be regenerated in its original form with reactions involving vitamin C, glutathione and lipoic acid. Antioxidant capabilities of α-tocopherol depend on the concentration of those compounds which maintain α-tocopherol in reduced state in cases of oxidative stress. It is possible that ROS over-production can cause significant decrease of active vitamin E concentration in tissue. α-tocopherol is discovered in lens, aqueous humour and retina (Penn et al., 1992).

Carotenoid lutein, zeaxathin and meso-zeaxanthin form macular pigment (MP). Their role is to act as antioxidants and protectors of photoreceptors (rods and cones) from blue light (Lawrenson et al., 2019).

The biggest concentration of carotenoid is in the plexiform layer of macula; zeaxathin dominates in the inner part of the macula - fovea, while lutein is spread in the peripheral part of retina (fig. 3). This is the reason why zeaxanthin is more efficient as an antioxidant in the area where risk from oxidation is more likely to happen (Handelman et al., 1988). The concentration of zeaxanthin in fovea is 2.5 times greater than lutein (Widomska et al., 2020).Both carotenoids are present in photoreceptors outer segment: rods and cones which are rich with docosahexaenoic acid (DHA) and are potentially sensitive to lipid oxidation (Carneiro et al., 2015). DHA composes 60% of photoreceptors lipidic membrane and represents a main structural lipid of retina (Souided et al., 2013). DHA can be synthetized

from eicosapentaenoic acid (EPA) and its main source comes from diet. Health benefits come from the ability of DHA and EPA to reduce the production of inflammatory eicosanoids, cytokines and ROS (Calder, 2009) and modulation of many gene expression which are involved in inflammation (Bouwens et al., 2009). Anti-inflammatory effects can inhibit the production of new choroidal vessels which can be visible in exudative AMD (Querques et al., 2014). Omega-3 fatty acids (EPA and DHA) are delivered to photoreceptor membranes through RPE. Every disbalance in the lipids of photoreceptors can contribute to the production of drusen in the layers of RPE (Carneiro et al., 2017) which are the beginning of changes related to AMD.

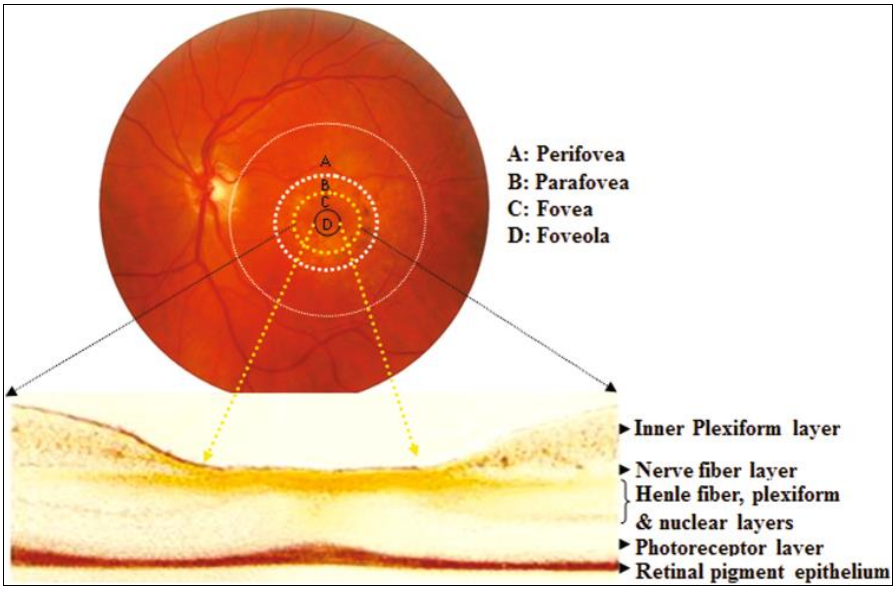


Fig. 3. Topography of macular pigment, schematic view of the distribution of yellow macular pigment on retina: horizontal (up) and vertical section (down) (taken from Arunkumar et al., 2018)

Supplements and AMD

There is evidence from randomized clinical studies that prophylactic intake of antioxidants in the form of vitamins and minerals does not prevent the development of AMD. Five big randomized clinical studies compared the intake of supplements containing vitamin E, beta-carotene, vitamin C or antioxidant combination of vitamins with placebo. The studies randomized more than 75.000 people and tracked their clinical results between 4 and 10 years. It is discovered that people who take the supplements have the similar risk of AMD development as those who do not take the supplements (Ewans et al., 2017).

Many randomized clinical studies also tackled the question of whether or not high dosages of antioxidants in the form of vitamins and minerals can slow down the AMD progression (Ewans et al., 2017). The majority of studies attracted small number of participants and were relatively short in duration, the span from 9 months up to 6 years. However, one big, multicentricrandomized clinical study conducted in the USA, age-related eye disease study -AREDS, randomized 3640 individuals with AMD and had them take supplements to the formulations which contain combination of vitamin C, E, beta-carotenes, zinc or copper or placebo each day. The main conclusion was that daily, long-term supplementation of vitamin C (500 mg), vitamin E (400 international units (IU)), beta-carotene (15 mg), zinc (80 mg, in the form of zinc oxide) and copper (2 mg, in the form of copper oxide) decreases the relative risk of AMD progression to the late stage (Lawrenson et al., 2019). The result achieved with patients who joined the study at later stages of diseases, to be more precise intermediate stage, up to more advanced stages, is 25% progression decrease in 5 years, while the effect on the patients in the early stages is still unknown. Besides AREDS, Report No8 concludes that patients with noncentral geographic atrophy also have the benefits of taking antioxidants and zinc.

Since it is established that smokers have increased incidence of lung carcinoma, the next AREDS2 study showed that removing beta-carotenes or lowering the dosage of zinc in the formula does not have the impact on the progression to the late stage of AMD (ČajkušićMance et al., 2019). Increased incidence of

lung carcinoma is recorded with patients who took AREDS formula as opposed to ones who took AREDS2 formula, especially with former smokers due to high dosages of beta-carotenes. Primary AREDS2 analysis showed that adding lutein and zeaxanthin and/or omega-3 fatty acids in the AREDS formula is not linked to significant reduction of risk of late-stage AMD progression in comparison to the original supplement (AREDS formula). Lutein and zeaxanthin are carotenoids which are main components of macular pigment. They have protective role in retina due to their antioxidant properties and abilities to act as filters of blue light. The analysis of AREDS2 suggested that lutein and zeaxanthin can be useful in the reduction of AMD progression if they are taken without beta-carotenes (Lawrenson et al., 2019).

Lutein, zeaxanthin and meso-zeaxanthin form macular pigment (MP). Lutein is precursor of meso-zeaxanthin and recently RPE65 is identified as an isomerase enzyme responsible for conversion of lutein to meso-zeaxanthin in RPE of vertebrate (Shyam et al., 2017). MP's primary function is lowering the dispersion of blue light in inner retina, and dark yellow color and anatomic position of MP are considered to be ideal for protection of foveal region from photo-oxidative damages (Arunkumar et al., 2018). Lutein filters blue light more efficiently than zeaxanthin and meso-zeaxanthin due to its orientation in lipid bilayer (Sujak et al., 1999). Many studies speak in favor of protective antioxidant abilities of carotenoid which are part of MP. Barker et al. (2005) in their study conclude that primates which are, from their birth, fed with food without carotenoid, are more prone to damages resulting from blue light. Photoreceptor cells are more prone to oxidation in comparison to other cells of retina because they contain a lot of polyunsaturated fatty acids in the membrane structure and lean on carotenoid in protection of oxidation stability. Chucair et al. (2007) showed that retinal neurons in rats which were treated with macular carotenoids have greater protection from oxidative stress then untreated group. With identification of lutein and zeaxanthin oxidative metabolites in retina, Khachik et al. (1997) further support the function of macular pigment in oxidative protection of retina.

Previous studies showed that individuals who are using computers or smartphones longer than 6 hours per day had the benefits from supplementation of carotenoids, not only in increased visual efficiency but also in better quality of sleep, reduction of headaches, eye fatigue and photophobia. Thus, supplementation of macular pigment in certain form can be beneficial even to those who are not suffering from AMD (Arunkumar et al., 2018).

The benefits of polyphenols in AMD include other antioxidant mechanisms besides removal of ROS. Dietary polyphenols (phenols) are numerous and heterogeneous groups of chemicals found in plants and beverages. They can be categorized in several groups and according to chemical structure, can be divided into following groups: phenolic acids (benzoic and cinnamic acid), flavonoids (isoflavonoids, neoflavanoids, chalcones, flavones, flavonoids, proanthocyanins, anthocyanidins). Other bioactive polyphenols, also important for the health of humans, are curcumin, resveratrol and ellagic acid (Pawlowska et al., 2019). Polyphenols show effects against aging, and therefore can be considered as preventative compounds in diseases related to aging which are usually induced by chronic oxidative stress and accumulation of their products (Khurana et al., 2013).

Bioavailability of polyphenolic compounds in human eye can be high. In perfusion system of rats in situ, bioavailability of quercetin was 20% of applied dosage (Crespy et al., 2003). High bioavailability of anthocyanins is recorded in ocular tissues after different ways of applications (Kalt et al., 2008). These and other reports suggest that flavonoids, including quercetin and anthocyanins can surpass the blood-retina barrier after oral application, as well as after acute intravenous and intraperitoneal application (Pawlowska et al., 2019).

So far, no therapy has been approved or confirmed for the treatment of geographic atrophy of severest form of "dry" AMD which represents subtype of late-stage AMD, while wet form of AMD is treated moderately successful with inhibitors of vascular endothelial growth factor (anti-VEGF). Multiple studies are currently searching for effective way of treating dry form of AMD.

In connection to that, it is known that quercetin inhibits choroidal neovascularization (CNV) induced by laser radiation in the eyes of rabbits in vivo and in vitro (Zhuang et al., 2011). This flavonoid improved the blood flow of choroidea and reduced migration of umbilical vein endothelial cells during the wound healing. Therefore, it can be considered that quercetin improves anti-VEGF therapy which is the only effective treatment of wet form of AMD (Sulaiman et al., 2014). Patients suffering from wet form of AMD receive a number of intravenous injections against VEGF but there are signals that anti-VEGF treatment can potentially increase the development of geographic atrophy (Gementzi et al., 2017). The most used Bevacizumab (Avastin) has side effects because it neutralizes all VEGF extracted

from RPE cells, which leads to disbalance in RPE homeostasis (Ford et al., 2011). Namely, VEGF is necessary for maintenance of retinal structure. Subramani et al. (2017) proved that combined activity of Bevacizumaba and resveratrol only partially neutralized extracted VEGF in ARPE-19 cells in comparison to cells which were treated individually with Bevacizumaba, when it came to neutralization of all VEGF. Resveratrol also showed synergistic protective effects together with zeaxanthin (Pawlowska et al., 2019). Park et al. (2017) state that antiapoptotic effect of curcumin extract (*Curcuma longa L., Zingiberaceae*) and its curcuminoids on cytotoxicity caused by exposure of ARPE-19 cells previously filled A2E to blue light. Similarly, polyphenolic components of *Vaccinium uliginosum* extracts containing flavonoids, anthocyanidins, phenylpropanoids and iridoids decrease ARPE-19 cell death caused by A2E photooxidation (Lee et al., 2016). *Vaccinium uliginosum L., Ericaceae* represent black or bog blueberry. Anthocyanidins in wild blueberries contribute to health of eyes, and cyanidin-3-glucoside in blueberries represent functional food for prevention of diseases related to retina (Wang et al., 2017). Many studies showed the protective effect of polyphenols found in blueberries on the retinal damages induced by light with lipid peroxidation (Ma et al., 2018).

Average level of zinc in the complex RPE - choroidea in patients suffering from AMD is reduced by 24% in comparison to others without AMD. Average level of copper in the complex RPE - choroidea in patients suffering from AMD is reduced by 23% in comparison to others without AMD, even though there was no difference in the levels of zinc or copper in the retina of people which have and don't have AMD. These results in combination with other information that oral supplementation of zinc and copper decreases the risk of AMD progression, suggests that homeostasis of these minerals play a role in AMD and retinal health (Erie et al., 2009).

Diet and AMD

Mediterranean diet, rich with whole grains, fresh season vegetables and fruits, beans, olive oil, nutty fruits, fish, herbs and red wine is tested in randomized controlled clinical research in order to show the beneficial effects in mitigation of cardiovascular diseases. It is discovered that Mediterranean diet is linked to a reduce risk of suffering from AMD. It is known that specific nutritious substances such as lutein and zeaxanthin found in leafy green vegetables, such as kale, are linked to a reduced risk of suffering from AMD. Fish is another important component of Mediterranean diet linked to a reduced risk of suffering from AMD and it is recommended to have fish two times per week (Chew, 2020).

Western diet is linked to a greater prevalence of AMD. Vegetable oils and animal fats containing omega-6 fatty acids, and red and refined meat needs to be consumed minimally in order to reduce the risk of AMD progression. Diet with high glycemic index and alcohol consumption of more than two drinks per day showed connections with AMD (Chapman et al., 2019).

Examination of the fundus which corresponds to the intermediate stage of AMD will in 50% of cases, during the next five years, and in 71% of cases, in the next ten years, advance to the late stage of AMD (Čeklić et al., 2015). Owing to the protective effect of vitamin C, E, carotenoid; lutein and zeaxanthin, polyphenols, zinc and copper, which can be taken with diet and above all Mediterranean diet and/or dietary supplements can reduce the risk of AMD progressing to late stages.

The recommendation regarding Mediterranean diet are intake of food rich with antioxidants and biologically active components, and reduced intake of saturated fatty acids and ingredients with higher glycemic index.

Biologically active components of food are non-nutritive and nutritive ingredients, and they have beneficial effect on health if consumed moderately. These include already mentioned polyphenolic compounds; resveratrol found in the grape skin, red wine, blueberry, raspberry and mulberry, quercetin found in onion and apples, curcumin found in ginger, safflower, curcumin, anthocyanins in blueberry (Jašić, 2010). Their positive effects are especially visible in neovascular AMD whether supporting the effects of anti-VEGF therapy such as quercetin or decreasing side effects caused by anti-VEGF therapy in case of resveratrol (Pawlowska et al., 2019). Besides polyphenolic compounds, under biologically active components we will include carotenoid, beta-carotene found in sweet potato, carrot, leafy green vegetables, apricot, peaches then xantofils; lutein found in goji berries, spinach, kale, eggs; zeaxanthin found in corn and eggs. Omega-3 fatty acids are also included in biologically active components, and their main sources are blue fish (pilchard, mackerel, salmon, cod, tuna), seeds (flex seeds, chia and sesame seeds) and nutty fruits (nuts, hazelnut, almond) (Jašić, 2010).

Oxidative stress which has an important role in pathogenesis of AMD can be increased with improper diet (Pawlowska et al., 2019).

Adherence to Mediterranean diet is connected to reduced risk of drusen growth which can have a beneficial effect in all stages of AMD.Variable factors, such as healthy diet, could play and important role in delaying the progression of early stages of AMD (Merle et al., 2020).

This would suggest that it is never too early or too late to accept healthy diet such as Mediterranean one. It is especially beneficial for geographic atrophy for which we do not have proven therapy and because AREDS2 supplements have beneficial effect on persons with neovascular AMD.

It appears there is a dosage-answer relationship; therefore, the more we adhere, the greater reduction of progression to late stages of AMD (Chew, 2020).

Diet rich with polyphenols has beneficial effects on many factors of risk related to AMD such as obesity, hypertension and hypercholesterolemia and it is proven that healthy diet reduces genetic risk of obesity (Pawlowska et al., 2019).

Choosing Mediterranean diet and physical activity and avoiding smoking and sedentary lifestyle can reduce the prevalence of early AMD, number of individuals developing advanced AMD and consequently reduce the burden on healthcare system which is caused by the treatment of this disease (Carneiro et al., 2017).

Study conducted in Japan proves the effects of diet. It involved 161 subjects with neovascular AMD and 369 subjects pertaining to control group. Subjects filled out a questionnaire about how frequent they consume 58 ingredients in the last month. Analysis of their dietary habits proved many claims about the connection between frequency of consumption of omega-3 fatty acids, vitamin E, zinc, vitamin D, vitamin C and beta-carotenes and neovascular AMD.

They proved reversed connection between consumption of omega-3 fatty acids and neovascular AMD. However, not a single study researched the effect of higher dosage intake of omega-3 fatty acids than those included in typical Japanese diet on neovascular AMD. Blue Mountains Eye Study (Australia) showed the protective effect of omega-3 fatty acids in late AMD, among those with highest quintile intake. Participants in AREDS which reported highest intake of omega-3 fatty acids also had significantly lower probability for neovascular AMD. However, in AREDS2, adding DHA + EPA to original formulation has not additionally reduced the risk of AMD. As already discussed, the cause of that could be inadequate dosage or inadequate length of treatment or both (Aoki et al., 2016).

In Japan, there was a descending trend between zinc intake and neovascular AMD which further supported the claim about protective effects of zinc on neovascular AMD. It should be noted that high dosage of zinc (80 mg zinc oxide), which can only be achieved with supplementation, in AREDS is enough to reduce the risk of neovascular AMD progression.

The same study showed that the vitamin E and vitamin C intake is linked to reduced risk of neovascular AMD. However, it appears that there is a limit and further studies which would involve more subjects in order to determine whether or not vitamin C is enough to reduce the risk of neovascular AMD are needed. AREDS showed that high dosage of vitamin C and E and beta-carotenes is not enough. It is required to add zinc in order to reduce the risk of neovascular AMD and the dosage of 400 IU of vitamin E recommended by AREDS is 13 times higher than the recommended daily allowance -RDA. Such levels of vitamin E can only be reached with supplementation (Aoki et al., 2016).

It is discovered in several studies that vitamin D reduces the risk of early AMD and has anti-inflammatory properties (Pahlet et al., 2013). Numerous genes included in inflammatory response are connected with AMD. Current study showed that vitamin D is linked to neovascular AMD. Fish is a source of vitamin D as well as omega-3 fatty acids (Nakamura et al., 2002), therefore increased intake of fish can be confusing factor because it is not known whether the positive effect comes from vitamin D or omega-3 fatty acids.

Lastly, by using the short questionnaire about the dietary history, they showed that the high intake of omega-3 fatty acids, vitamin E, zinc, vitamin D, vitamin C and beta-carotenes is linked with reduced risk of AMD (Aoki et al., 2016).

Conclusion

AMD is an important cause of vision loss globally. Therefore, it is really important to recognize the risk factors which can be influence on such as smoking, obesity, atherosclerosis and improper diet. Proper diet, above all Mediterranean diet rich with antioxidants, minerals, vitamins and polyphenols has certain beneficial effect on prevention and progression of AMD, which is the reason consultations regarding proper diet and supplementation is needed during eye examination of people at risk.

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