DOI: 10.24292/01.OT.350324.6

Supplementation in diet of patients with retinal diseases

Anna Święch[1], Sławomir Teper[2], Maciej Gawęcki[3], Anna Nowińska[2], Małgorzata Figurska[4], Joanna Adamiec-Mroczek[5], Izabella Karska-Basta[6], Jan Kucharczuk[7]

[1] Department of Retinal and Vitreous Surgery, Medical University of Lublin
Head: prof. Jerzy Mackiewicz, MD, PhD

[2] Chair and Clinical Department of Ophthalmology, School of Medical Science in Zabrze, Medical University of Silesia in Katowice
Head: prof. Edward Wylęgała, MD, PhD

[3] Department of Ophthalmology, Specialist Hospital in Wejherowo
Head: Maciej Gawęcki, MD, PhD

[4] Department of Ophthalmology, Military Institute of Medicine in Warsaw
Head: prof. Marek Rękas, MD, PhD

[5] Department and Clinic of Ophthalmology, Wroclaw Medical University
Head: prof. Marta Misiuk-Hojło, MD, PhD

[6] Department of Ophthalmology, Collegium Medicum, Jagiellonian University, Kraków
Head: prof. Bożena Romanowska-Dixon, MD, PhD

[7] Laboratory of Retinal Diseases, 10th Military Clinical Hospital with Polyclinic in Bydgoszcz
Head: Jan Kucharczuk, MD, PhD

HIGHLIGHTS

Proper supplementation should be administered in patients with initial stages of retinal diseases but as well as adjunctive procedure in exudative forms.

ABSTRACT

Etiology of retinal diseases, such as age-related macular degeneration or diabetic retinopathy is multifactorial, where oxidative stress and inflammation play an important role. Therefore supplementation of diet in that group of patients with proper product, which contains substances with anti-oxidant and anti-inflammatory properties is advised for reducing the risk of progression of such diseases.

Key words: supplementation, diet, retinal diseases, AMD, diabetic retinopathy

INTRODUCTION

Age-related macular degeneration (AMD) is one of the leading causes of vision loss in developed countries, including Poland and it globally affects nearly 9% of the population aged 45–85 years. In 2015, AMD was the fourth cause of blindness worldwide and the third cause of moderate-to-severe vision impairment. The number of AMD patients in Europe is growing steadily, presenting a significant challenge for the public health system. Patients with AMD experience a serious reduction in quality of life due to visual impairment.

There are two forms of AMD: wet and dry The dry form of AMD accounts for about 85–90% of all cases. The wet form is less common and occurs in about 10–15% of people with AMD. This progressive disease is characterized by degeneration of the retinal pigment epithelium (RPE), which leads to photoreceptor death and loss of central vision. Pigment epithelial cells are susceptible to oxidative stress – a factor that induces inflammation. Dry AMD is characterized by the presence of drusen, i.e., metabolic products accumulating under the retinal pigment epithelium, as well as thickening of the Bruch's membrane. Some patients with dry AMD may develop geographic atrophy with discrete areas of RPE loss, and the degeneration of photoreceptors and choroidal capillaries.

The wet form of AMD is characterized by the presence of choroidal neovascularization (CNV). The formation of the subretinal neovascular membrane occurs through pathological angiogenesis. Vascular endothelial growth factor (VEGF) plays a major role among the factors that activate this process.

The golden standard for treating wet AMD is intravitreal injections of anti-VEGF inhibitors. It aims to inhibit the formation of new vessels in the subretinal space. Unfortunately, there is currently no effective therapy for treating dry AMD.

The etiology of AMD is not yet well understood. Based on the available epidemiological studies, it was found to be multifactorial. In addition to aging-related processes, genetic predisposition and certain environmental factors such as smoking, diet, ultraviolet radiation and comorbid cardiovascular conditions are believed to be important [1, 2].

The relationship between dietary habits and therapeutic outcomes in patients with dry AMD is still under investigation. The largest multicenter, randomized clinical trials on the role of supplements in the diet of AMD patients conducted on more than 4,000 people are the AREDS (Age-Related Eye Disease Study) and AREDS2 studies. The results of the initial AREDS study, published in 2000, showed that the combination of dietary supplements included in the AREDS formula: vitamins C (500 mg) and E (400 mg), copper oxide (2 mg), zinc (80 mg) and β-carotene (15 mg), taken daily, orally, reduced the risk of progression to late AMD by 25%. A subsequent study (AREDS2), published in 2013, followed up about 70% of those participating in the previous randomized AREDS trial. β-carotene was removed from the original AREDS formulation due to its potential carcinogenicity in smokers, and the dose of zinc was reduced to 25 mg. The new formulation was enriched with omega-3 acids: DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid), lutein and zeaxanthin. The average duration of the study was 5 years. Participants were divided into 4 groups. In each group, the study participant took the formula with the modified AREDS formula and in addition, in group 1: lutein (10 mg) with zeaxanthin (2 mg); in group 2: DHA (350 mg) with EPA (650 mg); in group 3: lutein (10 mg) with zeaxanthin, DHA (350 mg) with EPA (650 mg); in group 4: placebo. The risk of progression to late AMD during 5-year follow-up in each group was estimated at: 31% in the group taking placebo, 29% in the group with lutein and zeaxanthin supplementation, 31% in the group taking DHA with EPA, and 30% in the group of study participants taking lutein, zeaxanthin, DHA and EPA. There was no apparent effect of β-carotene elimination or lower doses of zinc on AMD progression compared to the original AREDS formulation.

The addition of DHA and EPA had no additional effect on reducing AMD progression compared to the control group [3, 4].

VITAMIN D

Vitamin D precursor is produced mainly (about 80–100%) in the skin. It is formed under the influence of ultraviolet (UV) light through the conversion of the precursor 7-dehydrocholesterol (7DHC) into vitamin D_3. The amount of vitamin D produced in humans fluctuates seasonally. In a temperate climate zone, the amount of sunlight provided for nearly half the year is too low for human skin to produce enough of this vitamin on its own. An alternative source of vitamin D is a diet providing about 20% of its daily requirement. There are two forms of vitamin D in foods: animal-derived cholecalciferol (vitamin D_3), and plant-derived ergocalciferol (vitamin D_2). The former, absorbed in the small intestine, is transported to the liver and bound to DBP (vitamin D binding protein). The first step in the biosynthesis of the active form of vitamin D takes place in the liver. After enzymatic hydroxylation, vitamin 25-(OH)D is formed. This reaction is catalyzed by 25-hydroxylase (CYP27A1, CYP3A4 and CYP2R1), which is a group of hydroxylases included in cytochrome P450. Vitamin 25-(OH)D is transported to the kidneys, where the active form of vitamin D, 1α25(OH) 2D (calcitriol), is formed with the participation of 1α-hydroxylase (CYP27B1). Calcitriol belongs to a broad group of hormones that are gene transcription factors for

target proteins. The mechanism of action of calcitriol is mediated by the intracellular vitamin D receptor (VDR). The discovery of this receptor in many tissues has sparked research into other, non-classical, extraskeletal functions of vitamin D.

Vitamin D_3 has been recognized as an immunomodulating hormone. It regulates innate and acquired immune responses. Calcitriol in vitro inhibits the production of pro-inflammatory cytokines by CD4+ T cells and induces the phenotype of regulatory T cells. Endogenous conversion of $25(OH)D_3$ has been shown to inhibit dendritic cell antigen presentation and chemotaxis.

Vitamin D is a modulator of the immune system and interacts with two members of the H and I family regulators of complement activation. Calcitriol is thought to modulate the adaptive immune response to suppress inflammation. In addition, it reduces the production of pro-inflammatory cytokines by immune cells, inhibits the maturation of dendritic cells, and the proliferation of T and B lymphocytes. In 2015, Millen et al. described a synergistic effect between vitamin D levels and the expression of complement cascade proteins. The researchers further demonstrated that polymorphisms of proteins required for activation of the complement cascade increased the risk of AMD. An approximately 6-fold increase in the likelihood of AMD in women with vitamin D deficiency (<30 nmol/l) and 2 risk alleles for complement factors H and I have been observed compared to women who do not carry the high-risk alleles and have adequate vitamin D levels (>75 nmol/l) [5].

In the elderly (>65–75 years of age) and in dark-skinned individuals, due to reduced efficiency of skin synthesis, year-round supplementation with vitamin D is recommended at a dose of 800–2000 IU/24 h depending on body weight and dietary intake of the vitamin. In the oldest age group (>75 years of age), due to reduced efficiency of cutaneous synthesis, potential malabsorption, and altered vitamin D metabolism, year-round supplementation at a dose of 2000–4000 IU/24 h is recommended, depending on body weight and diet. In Poland, skin synthesis of vitamin D can be effective only in spring and summer (May to September). However, sun exposure in much of the adult population is usually very limited due to the type of performed work [6, 7].

CAROTENOIDS: LUTEIN AND ZEAXANTHIN

There is no de novo synthesis of lutein in the human body; it is only supplied with food. Carotenoids are fat-soluble, thus high-fat diets facilitate their absorption. Once these compounds are delivered and dissolved in gastric juice, they are absorbed as micelles. Transport is mainly through low-density lipoproteins (LDL) – 55%, high-density lipoproteins (HDL) – 33% and very low-density lipoproteins (VLDL) – 10–19%. The distribution of lutein and zeaxanthin in LDL and HDL is similar. A cross-sectional study published in 2012 observed an association between lutein and zeaxanthin concentrations and lipoprotein levels. In addition, it has been found that altering lipoprotein concentrations can affect lutein and zeaxanthin concentrations in the retina [8]. The transport of lutein into various human tissues is not uniform. Lutein and zeaxanthin in the human body are particularly concentrated in the macula, where they are the main component of the macular pigment of the retina. A recent study using confocal microscopy shows the spatial distribution of lutein and zeaxanthin in the human retina. Zeaxanthin has been shown to be concentrated in the fundus, extending from the inner to the outer limiting membrane, with particularly high concentrations in the outer plexiform layer. Zeaxanthin concentration drops sharply in the peripheral part of the fovea. Lutein, on the other hand, is more evenly distributed in the macula at a relatively lower concentration compared to zeaxanthin.

Due to the presence in its structure of hydroxyl groups in the carbon ring, lutein is characterized by higher polarity than other carotenoids. This structure allows it to better bind to oxygen in the serum.

Lutein and zeaxanthin act as a kind of high-energy filter for blue light, protecting the macula from photo-oxidative damage. It was shown that fluorescence emission in carotenoid-containing liposomes was lower than in carotenoid-free control samples after exposure to blue light, indicating a filter effect. Such effect was highest for lutein, followed by zeaxanthin, and to a lesser extent β-carotene. This is of great importance these days, as our eyes are particularly exposed to toxic blue light from smartphones, computers and the increasingly common LED lamps used indoors [9].

Numerous studies confirm the anti-inflammatory properties of lutein and zeaxanthin. In vitro studies show that lutein inhibits the activation of pro-inflammatory molecules such as: NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), as well as the expression of iNOS (inducible nitric oxide synthase) and cyclooxygenase 2 (COX-2), and may affect the levels of factor D of the complement activation pathway, involved in the pathogenesis of AMD [10, 11]. Lutein and zeaxanthin further attenuate the expression of genes associated with inflammation. There is evidence of a possible beneficial role for lutein in enhancing glial cell survival after hypoxia-induced damage via regulation of both apoptosis and autophagy [11].

Lutein is generally recognized as safe, as indicated by numerous studies, but there is a lack of conclusive data on its optimal dosage as a dietary supplement. High concentrations of lutein are found in dark green leafy vegetables and in egg yolk. The ratio of lutein to zeaxanthin varies between foods, ranging from 12 to 63 in green vegetables and only 0.1 to 1.4 in yellow-orange fruits and vegetables [12].

American adults typically consume about 1–2 mg of lutein per day. A systematic risk assessment of the use of lutein supplements in placebo-controlled intervention studies was published in 2006. It provided evidence that lutein is safe at doses up to 20 mg/24 h. Doses of lutein ranged from 8 to 40 mg/24 h, and the duration of the study ranged from 7 days to 24 months. Only a few studies monitored possible adverse side effects. AREDS2 study results reported no side effects except for some yellowing of the skin. This occurred with lutein and zeaxanthin supplementation (10 and 2 mg/24 h, respectively) for an average of 5 years in patients with intermediate AMD [13–15].

OMEGA-3 ACIDS

Omega-3 acids are unsaturated fatty acids. These include EPA and DHA. The human body is unable to produce them on its own. Their source is food, mainly marine fish. Omega-3 and omega-6 acids play a key role in the proper functioning of the brain and the process of cell growth and differentiation. Omega-3 acids are building blocks of phospholipids of cell membranes and mitochondrial membranes, microsomes, cells of the nervous system and retina of the eye. Many studies have demonstrated their anti-inflammatory, cardioprotective, hypotensive, anti-atherosclerotic effects, among others. The beneficial properties of DHA and EPA suggest a likely mechanism for regulating inflammatory and immune responses in the retina. There are many studies outlining the beneficial effects of omega-3 acids on reducing the risk of AMD. A study conducted in the United States on older male twins showed that frequent fish consumption and higher intake of omega-3 acids reduced the risk of AMD, even after accounting for other risk factors. Increased fish consumption at 2 or more servings per week reduced the risk of AMD. The protective effect of absorption of long-chain omega-3 polyunsaturated acids was evident only when the intake of linoleic acid (an omega-6 acid) was low. The authors found similar conclusions in other publications; they reported the need to maintain the right ratio of omega-6 and omega-3 acids in the diet. The ideal ratio of omega-6 to omega-3 is from 3:1 to 4:1,14. The results presented by Seddon et al. indicate that excessive amounts of omega-6 acids in the diet weaken the protective effects of omega-3 acids. In addition, cigarette smoking has been confirmed as a risk factor for AMD. Current smokers had an almost 2-fold increased risk of AMD, and past smokers had a 1.7-fold increased risk compared to those who had never smoked [4].

FOLIC ACID, VITAMINS B_6, B_{12}

Homocysteine (HCY) is an amino acid synthesized in the body from methionine and is an intermediate product in the synthesis of cysteine. The metabolism of homocysteine is closely related to the management of vitamins B_6, B_{12} and folic acid. Measurement of HCY levels is used in assessing the risk of atherosclerotic and thrombotic diseases. Elevated homocysteine levels in the blood cause, among other things, endothelial dysfunction, impaired vascular reactivity, and increased inflammatory processes. A deficiency of vitamins B_{12}, B_6 and folic acid is associated with an increase in HCY. An association between elevated serum homocysteine levels and an increased risk of AMD has been proven. A correlation was also observed between total intake of vitamin B_{12} and folic acid equivalent and the 10-year incidence of AMD. An increased risk of AMD over 10 years was significantly associated with baseline vitamin B_{12} or folic acid deficiency. In addition, vitamin B_{12} supplementation was associated with a reduced risk of AMD. Such association was independent of potential additional factors that could affect the outcome of the study, such as smoking, consumption of fish and other dietary supplements, and renal function parameters and white blood cell count. In the elderly, due to malabsorption, achieving optimal vitamin B_{12} concentrations can be problematic. A better option for the elderly are vitamin B_{12} supplements, which are taken in higher doses in crystalline form and are also more bioavailable than the naturally occurring vitamin [16].

ZINC

Zinc is an essential mineral found in the human body, as it acts as a catalyst for more than 300 enzymes. It plays an important role in the functioning of the immune and blood clotting systems, and is an important part of the body's antioxidant defense. Zinc has been shown to be involved in inhibiting complement activation and increasing the antioxidant capacity of the retina, which may play a protective role in AMD [17, 18]. A study conducted in Australia and published in 2019 by Dharamdasani Detaram et al. confirmed that reduced dietary zinc intake was associated with a higher likelihood of subretinal fluid and greater mean retinal thickness in patients with neovascular AMD during anti-VEGF treatment. A threshold effect for zinc was also observed, i.e., 8.1 mg, below which a higher risk of subretinal fluid was noted in the study group. However, zinc intake was not significantly associated with visual acuity [18].

VITAMINS C AND E

Vitamins C and E are mainly known for their antioxidant properties, involving the elimination of free radicals responsible for DNA damage. The AREDS study was designed to evaluate the effect of antioxidants and/or dietary zinc on the risk of developing advanced AMD. Participants were randomly assigned to one of four groups receiving appropriate oral preparations daily: group 1: antioxidants

(500 mg vitamin C, 400 IU vitamin E and 15 mg β-carotene); group 2: zinc (80 mg in the form of zinc oxide) and copper (2 mg in the form of copper oxide); group 3: antioxidants plus zinc; group 4: placebo. Individuals with extensive intermediate drusen, large drusen or non-central geographic atrophy in one or both eyes, or with advanced AMD or visual acuity <20/32 in one eye taking antioxidants in combination with zinc had the lowest risk of AMD progression or loss of visual acuity by 15 letters or more. The beneficial effect of antioxidants combined with zinc resulted in a 25% decrease in the relative risk of progression of AMD to its advanced form. In the group taking only antioxidants, the reduction in the risk of AMD progression was 17%, while it was 21% for those taking only zinc. The dose of β-carotene used in this study was 15 mg/24 h. Other studies using similar doses of β-carotene in individuals at high risk for lung cancer (cigarette smokers) have shown an increased incidence of cancer and death [15]. The study's safety monitoring committee recommended that smokers stop using β-carotene-containing drugs [19].

RESVERATROL

Due to its antioxidant power and ability to scavenge free radicals, resveratrol (RSV) can protect eye tissues from oxidative stress. The main targets of oxidative stress associated with AMD are the RPE cells, which form the cell layer responsible for maintaining the health of the retina by providing structural and nutritional support. Thanks to its antioxidant power, RSV may be as effective in reducing the risk of AMD as the antioxidants commonly found in fruits and vegetables (vitamins C, E and carotenoids), whose consumption has been shown to delay or prevent the development of retinal disease. In addition, the polyphenol protected against oxidative damage to RPE cells via a mechanism of modulation of SOD/MDA (malondialdehyde) activity and activation of Bcl-2 expression. These protective effects of RSV may be related to inhibition of mitogen-activated protein kinase (MAPK) pathways induced by oxidative stress. At the base level, RSV was able to reduce phosphorylation of extracellular signal-regulated kinase 1/2 (ERK 1/2) – phospho-ERK1/2, in a dose-dependent manner, as well as tyrosine/threonine mitogen-activated kinase (MEK), particularly at 25 and 50 μM RSV compared to cells treated with H_2O_2 alone.

In this approach to inhibiting angiogenesis, RSV may counteract AMD by affecting VEGF that contributes to abnormal blood vessel growth. To test this hypothesis, we tested the protective effect of RSV on oxysterol-induced VEGF secretion in RPE cells. Oxysterols induced VEGF-A secretion 24 h and 40 h after treating cells with 7β-hydroxycholesterol and 25-hydroxycholesterol, respectively. It was observed that simultaneous treatment of cells with RSV at a concentration of 1 μM reduced VEGF-A secretion induced by these oxysterols both after 24 h and after 40 h.

Resveratrol was also shown to inhibit macrophage infiltration into the RPE-vascular complex and to suppress the expression of inflammatory and angiogenic molecules, including VEGF, monocyte chemoattractant protein-1 (MCP-1) and intercellular adhesion molecule 1 (ICAM-1). The underlying molecular mechanism appears to be based on the maintenance of AMP-activated protein kinase (AMPK), which exerts NF-κB inhibitory effects in the RPE-vascular complex [20–22].

The 2023 study included 50 patients with wet AMD who qualified for anti-VEGF therapy (aflibercept 2 mg). Half of the subjects received a formula containing a set of supplements, including RSV (Resvega®, Laboratoires Thea). After analyzing the results obtained during the one-year follow-up, there were no significant changes in visual acuity in the two groups of patients, while an improvement in the sense of contrast was observed in the supplemented group. The authors also noted a significant difference in quality of life improvement based on patients' responses to the Hospital Anxiety and Depression Scale (HADS). It would undoubtedly be worthwhile to conduct a similar study with a longer follow-up period [20]. The findings presented in this paper suggest an important role for supplementation in patients with wet or dry AMD.

In another study [23], two groups of patients with unilateral wet AMD were observed; both groups received supplementation according to the AREDS protocol. The first group (59 study participants) – which was the control group – received supplementation according to the original AREDS formulation (vitamin C, vitamin E, β-carotene, zinc oxide), while the second group (50 persons) received supplementation according to AREDS, but excluding β-carotene, instead containing copper, DHA, lutein, zeaxanthin, RSV and hydroxytyrosol. Patients were studied after 6 and 12 months of supplementation. Analysis of the results showed that the use of an enriched supplement formula in the study group had no significant effect on visual acuity compared to the control group. However, there was a significant decrease in inflammatory cytokines, as well as a marked improvement in the fatty acid profile and an increase in serum lutein levels. This undoubtedly has a beneficial effect on the anti-inflammatory and anti-angiogenic profile of the AMD patient. Supplementation in patients with AMD has now become a routine procedure used by ophthalmologists in Europe; it should also be used in Poland.

The NAT2 (Nutritional AMD Treatment 2) study evaluated the prophylactic effect of orally administered DHA compared to placebo and observed a reduced risk of developing choroidal neovascularization in the study group. This was associated with an increased concentration of EPA/DHA acids in the cell membranes of red blood cells [24].

Another aspect that undoubtedly plays an important role in the complex etiopathogenesis of AMD is chronic inflammation, which is induced not only locally but also systemically in patients in this group. An increase in such inflammatory markers as IL-1 (interleukin 1), TNF (tumor necrosis factor), IL-6, CRP (C-reactive protein) is observed. The use of enriched supplementation in the study group resulted in a decrease in IL-8, IL-1 and TNF concentrations. This is important because both IL-1 and IL-8, as well as TNF, not only induce inflammation, but also have a stimulating effect on angiogenesis, so lowering the levels of these mediators reduces the risk of developing choroidal neovascularization, as has been documented in animal models.

Another ingredient in the AREDS-enriched formula, RSV, has an effect on reducing the secretion of pro-inflammatory cytokines such as IL-6, IL-8 and TNF.

In advanced stages of AMD, there is geographic atrophy or complications associated with subretinal neovascularization. In the dry form of AMD, patients are advised to take appropriate supplementation, as well as to use customized optical aids. Patients should also be sensitized to the issues of ensuring eye protection by wearing glasses equipped with ultraviolet radiation filters, stopping smoking, as well as maintaining a proper diet and physical activity.

In wet AMD, the standard therapeutic management is the administration of intravitreal injections with anti-VEGF inhibitors. A prerequisite for the success of this type of treatment is the regular administration of these drugs at intervals individually tailored to the needs of the individual patient.

Diabetic retinopathy is another disease that is one of the leading causes of vision deterioration and loss in the adult population. As with AMD, the etiology is multifactorial and includes, in addition to metabolic disorders, oxidative stress, inflammation, and changes initially involving the capillary endothelium. The effect of oral supplementation with antioxidants in patients with diabetic retinopathy was investigated and showed no significant effect on visual acuity or regression of diabetic macular edema. Instead, attention was drawn to the role of this type of supplementation, which in patients with the early stages of diabetic retinopathy is a valuable addition to the diet. Supplementation is recommended as a prophylactic measure in T1 and T2 stages of retinopathy and in patients with mild nonproliferative diabetic retinopathy without diabetic macular edema. As with AMD, improving the antioxidant and anti-inflammatory profile in this group is extremely important [21, 25].

In conclusion – it is worthwhile for patients with retinal conditions to recommend researched dietary supplements and a healthy lifestyle with limited UV exposure to the eyes. The improvement in a patient's anti-angiogenic and anti-inflammatory profile that follows the implementation of appropriately enriched supplementation is important due to the fact that both of these processes underlie most retinal diseases, led by AMD and diabetic retinopathy.

SUPPLEMENTATION VS. GENETICS

Macular diseases, especially AMD, are partly genetic. Currently, we do not have the ability to directly influence polymorphisms of genes that alter disease risk. This makes the area of research into the effects of specific supplement ingredients on preventing retinal damage all the more fascinating. Research to date is inconclusive, but the personalization of prevention can be expected to grow rapidly in the coming years with the spread of genetic testing and more population-based studies. It cannot be ruled out that artificial intelligence-based analysis of imaging studies will uncover such correlations in somewhat smaller groups of patients or sooner than after many years. The main difficulties in this type of research so far have been precisely both the necessary observation time and the very large size of the study population, as well as the multitude of confounding factors. Studies conducted on animal models and cell lines also provide valuable information.

Analysis of genetic variants in the AREDS study was associated with pharmacogenetic suggestions. Patients without CFH (complement factor H) risk alleles and with 1 or 2 ARMS2 (age-related maculopathy susceptibility 2) risk alleles obtained maximum benefit from zinc-only supplementation. Patients with 1 or 2 CFH risk alleles and no ARMS2 risk alleles received maximum benefit from supplementation containing only antioxidants; zinc treatment was associated with increased progression to advanced AMD. The results were supplemented 2 years after the first publication – the benefits of specific supplementation in certain genetic groups were indicated [17]. Interestingly, this was in response to the work of Chew et al. which indicated that supplementation efficacy was independent of genotype [26]. The work by Chew et al. divided the study population into 27 different genotypes, making it impossible to obtain significant results in any of the groups. In such a view, supplementation would by definition be ineffective in everyone, which is inconsistent with the available data of many studies. Therefore, it is worth recalling the recommendations from the aforementioned 2015 paper, which divided patients into only 4 groups according to genotypes:

1. We recommend zinc or an AREDS formulation containing zinc in patients with 0 or 1 CFH and 1 or 2 ARMS2 risk alleles.
2. We recommend antioxidants for patients with 1 CFH risk allele and 0 ARMS2. We predict that patients with 2 CFH risk alleles and no ARMS2 risk alleles would have a higher AMD progression rate with zinc or AREDS treatment and should be treated with antioxidants, which

is consistent with the observed 3-fold increase in AMD incidence over 7 years – progression associated with zinc or AREDS treatment.

3. Finally, for patients with 2 CFH risk alleles and 1 or 2 ARMS2 risk alleles, with the highest genetic risk, no treatment provides significant benefit [17]. Thus, should CFH and ARMS2 polymorphisms be mandated to be tested in the entire supplementation population? Genetic tests of this type are inexpensive and readily available. It seems that this stage of pharmacogenomics in AMD has not yet arrived. Post-hoc studies do not provide sufficient evidence for the conclusiveness of such recommendations. Instead, they point to the potential necessity of genotype-based prospective studies as early as the initial stages. Perhaps, by using genetically matched supplements, we could incorporate them into the diet earlier and prevent the development of AMD in most people. In selected groups of interested patients, a genetic test may be considered.

However, it is important to note that at least some of the nutrigenetic associations can be surprising and demonstrate the complexity of biochemical mechanisms. Among women taking at least 15 mg of zinc per day, there was a reduction in the risk of cognitive impairment if they carried 1 or 2 copies of the increased AMD risk polymorphism of the CFH gene, but no risk copy of the ARMS2 gene. In contrast, an increased risk of AMD has been reported in the same group [27].

Contrary to appearances, diabetic changes seen in the fundus are also not solely related to metabolic glycemic control, but also depend on genetic polymorphisms, which themselves can significantly worsen diabetic retinopathy. One example is the methylenetetrahydrofolate reductase gene (MTFHR), polymorphisms of which affect homocysteine levels and adversely alter the course of retinopathy. The common C677T polymorphism of the MTHFR enzyme causes impaired sensitivity to flavinadenine dinucleotide, reducing the synthesis of L-methylfolate. This causes elevated homocysteine levels, resulting in hypertension and vascular disease [28]. Riboflavin supplementation increases L-methylfolate synthesis, lowers homocysteine levels and lowers blood pressure, which appears to protect the retina from hyperglycemia and oxidative stress [29]. MTHFR polymorphisms also increase the body's susceptibility to vitamin B_6 deficiency [30, 31]. It was noted that hyperhomocysteinemia has probably an independent effect on AMD as well. In the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS), high doses of vitamins B_6, B_{12} and folic acid reduced the risk of developing AMD by 40% after 7 years [32].

The mechanisms involved in risk are not the sole determining factor; the metabolism of the substances taken also plays a role. Carotenoids used in supplements may be absorbed and utilized differently by the body, which could also be associated with personalized dietary recommendations in the future [33].

CONCLUSION

It is worth noting that the world's expert retinologists, affiliated with both European (e.g. EURETINA) and American (American Academy of Ophthalmology – AAO) associations, address the use of supplementation in affected patients in their guidelines for the treatment of retinal disorders. Based on the results of the AREDS study, supplementation with formulations that correspond to the AREDS formulation is recommended for a group of patients diagnosed with moderate or advanced dry AMD. The aforementioned associations point out the need for proper patient qualification and the use of appropriate supplements. Due to the wide availability and variety of such preparations and numerous advertisements in the media, a large group of patients use supplements whose composition significantly deviates from the recommended one. For this reason, it is extremely important to educate such individuals to make them aware of the legitimacy of using formulations tested for composition.

This task is one of the initiatives taken by a group of Polish specialists involved in the treatment of retinal disorders, affiliated with the newly established Retina Club Association.

CORRESPONDENCE
prof. Anna Święch, MD, PhD
Department of Retinal and Vitreous Surgery,
Medical University of Lublin
ul. Chmielna 1, 20-079 Lublin
e-mail: anna.zub@umlub.pl

ORCID
Anna Święch – ID – http://orcid.org/0000-0002-2238-6966
Sławomir Teper – ID – http:// orcid.org/0000-0002-0935-8880
Maciej Gawęcki – ID – http:// orcid.org/0000-0003-2901-0248
Izabella Karska-Basta – ID – http://orcid.org/0000-0001-7927-6277
Joanna Adamiec – ID – http://orcid.org/0000-0000-2680-4358X
Małgorzata Figurska – ID – https://orcid.org/0000-0002-6366-802X
Jan Kucharczuk – ID – http://orcid.org/0000-0001-8914-1798

References

1. Kauppinen A, Paterno JJ, Blasiak J et al. Inflammation and Its Role in Age-Related Macular Degeneration. Cell Mol Life Sci. 2016; 73: 1765-86. http://doi.org/10.1007/s00018-016-2147-8.
2. Klein R, Klein BEK, Tomany SC et al. Ten-Year Incidence of Age-Related Maculopathy and Smoking and Drinking: The Beaver Dam Eye Study. Am J Epidemiol. 2002; 156: 589-98. http://doi.org/10.1093/aje/kwf092.
3. Seddon JM, Rosner B, Sperduto RD et al. Dietary Fat and Risk for Advanced Age-Related Macular Degeneration. Arch Ophthalmol. 2001; 119; 1191-9. http://doi.org/10.1001/archopht.119.8.1191.
4. Seddon JM, George S, Rosner B. Cigarette Smoking, Fish Consumption, Omega-3 Fatty Acid Intake, and Associations with Age-Related Macular Degeneration: The US Twin Study of Age-Related Macular Degeneration. Arch Ophthalmol. 2006; 124: 995-1001. http://doi.org/10.1001/archopht.124.7.995.
5. Millen AE, Meyers KJ, Liu Z et al. Association between vitamin D status and age-related macular degeneration by genetic risk. JAMA Ophthalmol. 2015; 133(10): 1171-9. http://doi.org/10.1001/jamaophthalmol.2015.2715.
6. Renzi LM, Hammond BR, Dengler M et al. The Relation between Serum Lipids and Lutein and Zeaxanthin in the Serum and Retina: Results from Cross-Sectional, Case-Control and Case Study Designs. Lipids Health Dis. 2012; 11: 33. http://doi.org/10.1186/1476-511X-11-33.
7. An Update on Vitamin D and Human Immunity – Hewison – 2012 – Clinical Endocrinology – Wiley Online Library .
8. Li B, George EW, Rognon GT et al. Imaging Lutein and Zeaxanthin in the Human Retina with Confocal Resonance Raman Microscopy. Proc Natl Acad Sci. 2020; 117: 12352-8. http://doi.org/10.1073/pnas.1922793117.
9. Junghans A, Sies H, Stahl W. Macular Pigments Lutein and Zeaxanthin as Blue Light Filters Studied in Liposomes. Arch Biochem Biophys. 2001; 391; 160-4. http://doi.org/10.1006/abbi.2001.2411.
10. Bian Q, Gao S, Zhou J et al. Lutein and Zeaxanthin Supplementation Reduces Photooxidative Damage and Modulates the Expression of Inflammation-Related Genes in Retinal Pigment Epithelial Cells. Free Radic Biol Med. 2012; 53: 1298-307. http://doi.org/10.1016/j.freeradbiomed.2012.06.024.

11. Fung FKC, Law BYK, Lo ACY. Lutein Attenuates Both Apoptosis and Autophagy upon Cobalt (II) Chloride-Induced Hypoxia in Rat Műller Cells. PLOS ONE 2016; 11: e0167828. http://doi.org/10.1371/journal.pone.0167828.
12. Humphries JM, Khachik F. Distribution of Lutein, Zeaxanthin, and Related Geometrical Isomers in Fruit, Vegetables, Wheat, and Pasta Products. J Agric Food Chem. 2003; 51: 1322-7. http://doi.org/10.1021/jf026073e.
13. Age-Related Eye Disease Study 2 (AREDS2) Research Group; Chew EY, Clemons TE, Sangiovanni JP et al. Secondary Analyses of the Effects of Lutein/Zeaxanthin on Age-Related Macular Degeneration Progression: AREDS2 Report No. 3. JAMA Ophthalmol. 2014; 132: 142-9. http://doi.org/10.1001/jamaophthalmol.2013.7376.
14. Age-Related Eye Disease Study 2 (AREDS2) Research Group; Chew EY, SanGiovanni JP, Ferris FL et al. Lutein/Zeaxanthin for the Treatment of Age-Related Cataract: AREDS2 Randomized Trial Report No. 4. JAMA Ophthalmol. 2013; 131: 843-50. http://doi.org/10.1001/jamaophthalmol.2013.4412.
15. Chew EY, Clemons TE, SanGiovanni JP. et al. Lutein + Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration: The Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial. JAMA. 2013; 309: 2005-15. http://doi.org/10.1001/jama.2013.4997.
16. Gopinath B, Flood VM, Rochtchina E et al. Homocysteine, Folate, Vitamin B-12, and 10-y Incidence of Age-Related Macular Degeneration123. Am J Clin Nutr. 2013; 98: 129-35. http://doi.org/10.3945/ajcn.112.057091.
17. Awh CC, Hawken S, Zanke BW. Treatment Response to Antioxidants and Zinc Based on CFH and ARMS2 Genetic Risk Allele Number in the Age-Related Eye Disease Study. Ophthalmology. 2015; 122: 162-9. http://doi.org/10.1016/j.ophtha.2014.07.049.
18. Dharamdasani Detaram H, Mitchell P, Russell J et al. Dietary Zinc Intake Is Associated with Macular Fluid in Neovascular Age-Related Macular Degeneration. Clin Experiment Ophthalmol. 2020; 48: 61-8. http://doi.org/10.1111/ceo.13644.
19. Chew EY, Clemons TE, Agrón E et al. Long-Term Effects of Vitamins C and E, β-Carotene, and Zinc on Age-Related Macular Degeneration: AREDS Report No. 35. Ophthalmology. 2013; 120: 1604-11.e4. http://doi.org/10.1016/j.ophtha.2013.01.021.
20. Datseris I, Bouratzis N, Kotronis C et al. One-Year Outcomes of Resveratrol Supplement with Aflibercept versus Aflibercept Monotherapy in Wet Age-Related Macular Degeneration. Int J Ophthalmol. 2023; 16: 1496-502. http://doi.org/10.18240/ijo.2023.09.17.
21. Lançon A, Frazzi R, Latruffe N. Anti-Oxidant, Anti-Inflammatory and Anti-Angiogenic Properties of Resveratrol in Ocular Diseases. Molecules. 2016; 21: 304. http://doi.org/10.3390/molecules21030304.
22. Pop R, Daescu A, Rugina D et al. Resveratrol: Its Path from Isolation to Therapeutic Action in Eye Diseases. Antioxidants. 2022; 11: 2447. http://doi.org/10.3390/antiox11122447.
23. García-Layana A, Recalde S, Hernandez M et al. A Randomized Study of Nutritional Supplementation in Patients with Unilateral Wet Age-Related Macular Degeneration. Nutrients. 2021; 13(4): 1253. http://doi.org/10.3390/nu13041253.
24. Souied EH, Delcourt C, Querques G et al. Oral Docosahexaenoic Acid in the Prevention of Exudative Age-Related Macular Degeneration: The Nutritional AMD Treatment 2 Study. Ophthalmology. 2013; 120: 1619-31. http://doi.org/10.1016/j.ophtha.2013.01.005.
25. Alfonso-Muñoz EA, Burggraaf-Sánchez de las Matas R, Mataix Boronat J et al. Role of Oral Antioxidant Supplementation in the Current Management of Diabetic Retinopathy. Int J Mol Sci. 2021; 22: 4020. http://doi.org/10.3390/ijms22084020.
26. Chew EY, Klein ML, Clemons TE et al. No Clinically Significant Association between CFH and ARMS2 Genotypes and Response to Nutritional Supplements. Ophthalmology. 2014; 121: 2173-180. http://doi.org/10.1016/j.ophtha.2014.05.008.
27. Kustra R, Awh CC, Rojas-Fernandez C et al. CFH and ARMS2 Polymorphisms Interact with Zinc Supplements in Cognitive Impairment in the Women's Health Initiative Hormone Trial. J Alzheimers Dis. 2018; 66: 707-15. http://doi.org/10.3233/JAD-180673.
28. Neelam K, Goenadi CJ, Lun K et al. Putative Protective Role of Lutein and Zeaxanthin in Diabetic Retinopathy. Br J Ophthalmol. 2017; 101: 551-8. http://doi.org/10.1136/bjophthalmol-2016-309814.
29. McNulty H, Strain JJ, Hughes CF et al. Riboflavin, MTHFR Genotype and Blood Pressure: A Personalized Approach to Prevention and Treatment of Hypertension. Mol Aspects Med. 2017; 53: 2-9. http://doi.org/10.1016/j.mam.2016.10.002.
30. Hoogeveen EK, Kostense PJ, Eysink PED et al. Hyperhomocysteinemia Is Associated With the Presence of Retinopathy in Type 2 Diabetes Mellitus: The Hoorn Study. Arch Intern Med. 2000; 160: 2984-90. http://doi.org/10.1001/archinte.160.19.2984.
31. Kowluru RA, Mohammad G, Sahajpal N. Faulty Homocysteine Recycling in Diabetic Retinopathy. Eye Vis. 2020; 7: 4. http://doi.org/10.1186/s40662-019-0167-9.
32. Christen WG, Glynn RJ, Chew EY et al. Folic Acid, Pyridoxine, and Cyanocobalamin Combination Treatment and Age-Related Macular Degeneration in Women: The Women's Antioxidant and Folic Acid Cardiovascular Study. Arch Intern Med. 2009; 169: 335-41. http://doi.org/10.1001/archinternmed.2008.574.
33. Borel P. Genetic Variations Involved in Interindividual Variability in Carotenoid Status. Mol Nutr Food Res. 2012; 56: 228-40. http://doi.org/10.1002/mnfr.201100322.

Authors' contributions:
Anna Święch and Sławomir Teper: writing the article and completing the bibliography. Other contributors: critical revisions for important intellectual content and final approval of the version to be submitted.

Conflict of interest:
None.

Financial support:
None.

Ethics:
The content presented in the article complies with the principles of the Helsinki Declaration, EU directives and harmonized requirements for biomedical journals.