

THE ROLE OF VITAMINS IN THE TREATMENT OF AGE RELATED MACULAR DEGENERATION

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SUMMARY – The role of vitamins in the treatment of age related macular degeneration was reviewed. The following studies were selected for review: Eye Disease Case Control Study (EDCCS), Beaver Dam Eye Study, Blue Mountains Eye Study, Pathologies Oculaires Liees a l'Age Study (studija POLA) and Age Related Eye Disease Study (AREDS). These studies showed that antioxidant intake could be recommended in patients with certain forms of age related macular degeneration. A definite answer concerning the role of antioxidants is expected to be provided by additional studies.

Key words: *Macular degeneration – etiology; Macular degeneration – prevention and control; Antioxidants – metabolism; Antioxidants – administration and dosage; Diet*

Introduction

Age related macular degeneration (AMD) is the leading cause of vision impairment in people aged 65 and older¹. AMD is currently classified as follows: early forms of the disease are referred to as age related maculopathy and are characterized by soft drusen, pigmentary abnormalities (hyperpigmentation, hypopigmentation) or a combination of the two. Later forms of the disease are referred to as AMD, which can be further subdivided into dry AMD characterized by geographic atrophy, and wet AMD characterized by choroidal neovascularization, detachment of the retinal pigment epithelium or retinal scarring².

Patients suffering from late forms of the disease are unable to perform daily activities like reading, writing or driving a car, and are therefore dependent on others' help. The socioeconomic effects of this disease are becoming markedly important because of the increase in the population mean age.

Epidemiological studies have identified many risk factors^{3,4}, including heredity⁵⁻⁷, age³, iris color⁸, cardio-

vascular disease⁹, alcohol intake¹⁰, sunlight exposure¹¹, and smoking^{4,12-14}. In a number of studies, tobacco smoking has been shown to be the only preventable risk factor^{3,4} associated with either early or late AMD. At present, however, there is no known therapy to prevent or at least slow down the progression of the disease to more advanced forms. Laser photocoagulation¹⁵, photodynamic therapy¹⁶, and surgical procedures¹⁷ are only effective in a small number of patients, and then with a limited success. In addition, a number of studies have shown that oxidative damage may play a role in the pathogenesis of AMD¹⁸⁻²². Highly reactive oxygen radicals that are a byproduct of metabolism, cause damage to polyunsaturated fatty acids in cell membrane. Rods and cones in the retina are especially prone to this kind of damage because of their high content of polyunsaturated fatty acids and their constant exposure to light. Antioxidant vitamins such as vitamins A, C and E are able to block oxidative damage by quenching highly reactive oxygen radicals.

Lately there has been a lot of discussion over the possible protective role of vitamins and other antioxidant nutrients in the prevention or even treatment of AMD. The aim of this review is to summarize the most important studies (Table 1) dealing with the issue of prevention or treatment of AMD with antioxidants.

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Table 1. Basic characteristics of the studies reviewed

Study (year)	Study design/ population age (yrs)	No. of subjects	Antioxidants tested
EDCCS (1993)	Case control/55-80	421/615 controls	Vitamins C, E, α -carotene, β -carotene, lutein, zeaxanthin, lycopene, β -cryptoxanthin
Beaver Dam Eye Study (1996)	Retrospective/43-86	314/1968 controls	Vitamins C, E, α -carotene, β -carotene, lutein, zeaxanthin, lycopene, β -cryptoxanthin
Blue Mountains Eye Study (1999)	Cross-sectional/49	2900	Vitamins A, C, zinc, α -carotene, β -carotene
POLA (1999)	Prospective/60	2584	Vitamins C, E, β -carotene
AREDS (2001)	Randomized multicenter clinical trial	3640	Vitamins C, E, β -carotene, zinc

Eye Disease Case Control Study (EDCCS)

The Eye Disease Case Control Study¹⁹ was a case control multicenter study the goal of which was to assess the relationship between plasma concentration of antioxidants and the risk of neovascular AMD. The study included patients from five large clinical centers in the USA, i.e. 421 cases diagnosed with neovascular form of AMD and 615 controls. Fasting blood samples were obtained from all study subjects to measure serum levels of vitamins C and E, selenium, and carotenoids (lutein/zeaxanthin, β -carotene, α -carotene, cryptoxanthin, lycopene). The 20th and 80th percentile values were determined in the control group for each micronutrient individually and for pooled carotenoids. These percentiles allowed for determination of three scores for each variable: low (20th percentile and lower), medium (between 20th and 80th percentile), and high (80th percentile and higher). Odds ratios were calculated for each of the micronutrients individually and for pooled micronutrients. Statistical analysis showed each of the antioxidants alone to have no statistically significant protective effect on the development of neovascular AMD. The odds ratios for carotenoids (i.e. those for lutein/zeaxanthin, β -carotene, α -carotene and cryptoxanthin) ranged from 0.3 to 0.5 in subjects from the high percentile group vs those from the low percentile group ($p < 0.001$). However, the antioxidant index, which comprised combined antioxidant measurements, showed a statistically significant risk reduction in subjects from the high percentile group vs subjects from the low percentile group ($p = 0.005$).

Beaver Dam Eye Study

The Beaver Dam Eye Study²¹ was a retrospective study the goal of which was to assess the relationship between dietary intake of antioxidants and zinc, and the risk of early or late AMD. The study included 1968 subjects from Beaver Dam, Wisconsin, USA, 314 of them with early AMD and 30 with late AMD. The median daily intake of vitamins C and E, α -carotene, β -carotene, zinc, lutein, zeaxanthin, lycopene and β -cryptoxanthin was calculated using a special computer software. Study results showed the higher intake of zinc to be associated with a lower risk of early AMD. This finding was statistically significant ($p < 0.05$). A high zinc intake was not protective against late AMD but due to a small number of subjects with late AMD ($n = 30$) no definitive conclusions could be made. The intake of other antioxidants was unrelated to either early or late AMD.

Blue Mountains Eye Study

The Blue Mountains Eye Study²³ was a population based, cross-sectional study the goal of which was to assess the relationship between age related maculopathy and dietary intake of antioxidants deriving from diet, supplements, or both. Similar to the Beaver Dam Eye Study design, 3654 residents of the Blue Mountains region, west of Sydney, Australia, were randomly selected and included in the study. All study subjects were asked to complete a food frequency questionnaire indicating average consumption frequency of various food items, including vita-

mins A and C, carotene and zinc. Signs of early age related maculopathy were found in 240 subjects, and those of late age related maculopathy in 72 subjects. AMD lesions were classified using the Wisconsin Age-Related Maculopathy Grading System²⁴, which has been incorporated in an international classification². The Blue Mountains Eye Study failed to demonstrate any correlation between the antioxidant intake deriving from either diet or supplements, and AMD. The odds ratios for late AMD were 0.73 for carotene, 1.04 for zinc, 1.30 for vitamin C, and 1.22 for vitamin A. The odds ratios for early AMD were 0.66 for carotene, 0.79 for zinc, 0.86 for vitamin C, and 1.19 for vitamin A. None of these yielded a statistically significant tendency. The more so, the increasing intake of none of these antioxidants resulted in a decreased prevalence of AMD.

Pathologies Oculaires Liees a l'Age (POLA Study)

The POLA study²⁵ was a prospective study the goal of which was to evaluate the relationship between the levels of antioxidant nutrients and AMD. The study included 2584 residents of Sète, France. Fasting blood samples were obtained and plasma levels of cholesterol, triglycerides, and vitamins A, C and E were measured. In addition, red blood cell reduced glutathione (GSH) was also determined. Late AMD was diagnosed in 38 (1.8%) study subjects. The 20th and 80th percentile values were determined for each of the measured antioxidants to form three groups of quintiles: low, medium, and high quintile group. Odds ratios were calculated using the low quintile group as a reference. Results of the POLA study showed the subjects with high quintiles of α -tocopherol values to have a 50% decrease in the prevalence of late AMD (OR 0.50), however, this correlation did not reach statistical significance ($p=0.07$). The subjects with high quintiles of the α -tocopherol to lipid ratio had an 82% decrease in the prevalence of late AMD (OR 0.18; p for trend 0.003). The other antioxidants

tested (vitamin A, vitamin C, and red blood cell GSH) failed to show any significant correlation with late AMD.

Age Related Eye Disease Study (AREDS)

Unlike the studies mentioned above, the Age Related Eye Disease Study²⁶ was a randomized, placebo controlled study investigating the effect of high dose vitamins C and E, β -carotene and zinc supplementation on the progression of AMD. The doses of antioxidants were 5-15 times higher than the recommended daily allowance. A total of 4757 patients were enrolled in AREDS. They were divided into four categories based on the extent of fundus abnormalities (Table 1). As only five of 1117 category 1 subjects subsequently developed advanced forms of AMD, the effect of antioxidant intake could not be assessed in this group and they had to be excluded from statistical analysis. Thus, 3640 subjects continued the study, 1063, 1621 and 956 of them falling into category 2, 3 and 4, respectively. They all were randomized with 25% probability to one of the following interventional groups: placebo, antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and β -carotene, 15 mg), zinc (zinc oxide, 80 mg; and copper oxide, 2mg), or antioxidants plus zinc.

During the course of the study, two studies suggesting potential harmful effects of β -carotene in smokers were published^{27,28}. The smokers enrolled in AREDS were informed about the results of those studies, whereafter 72 participants were reassigned to the placebo group and 84 participants from the antioxidant group to a group without antioxidants. Statistical analysis was performed, and odds ratios and relative risk were calculated. Analysis of the data obtained in AREDS showed high dose supplementation to have no significant effect on the development of the late form of AMD or vision loss in categories 1 and 2. Thus, the results of treatment interventions were only relevant for categories 3 and 4. The 5-year probability of progression to advanced AMD was 20% in the antioxidant

Table 2. Categorization of AREDS patients

Category	Characteristics	No. of subjects
1	No drusen or few small drusen (<63 μ m)	1117
2	Multiple small drusen or few intermediate drusen (63-124 μ m) or pigment abnormalities	1063
3	Multiple intermediate drusen or large confluent drusen (>125 μ m) or noncentral geographic atrophy	1621
4	Advanced age related macular degeneration in one eye: geographic atrophy involving the center of macula or signs of choroidal neovascularization	956

and zinc group, 22% in the zinc group, 23% in the antioxidant alone group, and 28% in the placebo group.

According to these data, the risk reduction of AMD progression was significant in the group supplemented with antioxidants and zinc (OR 0.72; 99% confidence interval 0.52-0.98), suggestive in the group supplemented with zinc (OR 0.75; 99% confidence interval 0.55-1.03), and non-significant in the antioxidant group (OR 0.80; 99% confidence interval 0.59-1.09).

Another AREDS endpoint, i.e. visual acuity decrease by at least 15 letters (equivalent to visual angle doubling) showed similar results. The probability of vision loss was 23% in the antioxidant plus zinc group, compared with 29% in the placebo group. Accordingly, the risk reduction was statistically significant in the antioxidant plus zinc group (OR 0.73; 99% confidence interval 0.54-0.99).

Discussion

The studies reviewed herewith have shown that antioxidant intake is justified in patients with certain forms of AMD. The EDCCS has pointed out that carotenoids and combined antioxidant index are associated with a decreased prevalence of neovascular AMD. A potential bias in this study derived from the fact that cases with diagnosed neovascular AMD were 5 times more likely to start taking antioxidant supplements than controls in hope to slow down the progression of the disease.

Likewise EDCCS, the POLA study used serum measurements of antioxidants to assess the relationship between antioxidants and AMD. High levels of plasma vitamin E were found to be negatively associated with late AMD. However, an association between dietary vitamin E and incidence of large drusen was observed in only one of other studies²⁹. Four other studies found no association between vitamin E and AMD whatsoever^{19,21,30,31}. Furthermore, both EDCCS and POLA studies have shown similar limitations: serum antioxidant measurements do not necessarily reflect their dietary or supplement intake, since their metabolism can be very complex and involve many intermediaries. Therefore, the EDCCS and POLA investigators could not make definite recommendations concerning antioxidant intake. The Beaver Dam Eye Study and Blue Mountains Eye Study used a similar study design. These both were cross-sectional, population based studies where food frequency questionnaire was used to assess the antioxidant status and risk of AMD. The results reported from the Beaver Dam Eye Study indicated a weak association between zinc intake and early AMD, whereas

no association between AMD and dietary antioxidants has been reported from the Blue Mountains Eye Study. The reason for this may have been in the way of data collection. In the Blue Mountains Eye Study, dietary information pertained to current diet, whereas in the Beaver Dam Eye Study they referred to diet in the past (10 years). According to the Blue Mountains Eye Study investigators, past diet might be more relevant on assessing the risk of AMD than current diet, since the latter can be influenced by the publicity in mass media. Nevertheless, the authors found no obvious reason for finding no association between dietary antioxidant intake and AMD in the Blue Mountains Eye Study.

One can say that all these four studies lacked statistical power, mainly due to a small number of AMD cases and the fact that they were merely observational studies. This was the main motive to initiate AREDS, a randomized, placebo controlled study. The AREDS showed a beneficial effect of antioxidant and zinc supplementation in categories 3 and 4, i.e. in patients with moderate and advanced forms of AMD. Considering categories 1 and 2, i.e. patients with early AMD, the study was underpowered to reveal whether the supplementation had any beneficial effect. Although the doses of antioxidant and zinc supplement were 5-15 times higher than the recommended daily allowance, no serious side effects were recorded. During the study, two other studies suggesting an increased risk of bronchial carcinoma among smokers supplemented with β -carotene were published^{27,28}. Therefore, smokers or ex-smokers should be discouraged from taking AREDS formulation.

Several reports have recently appeared stating that lutein and zeaxanthin, two carotenoids that are primarily found in retina, might be a crucial element in protecting retina from oxidative damage³²⁻³⁵. Lutein and zeaxanthin cannot be synthesized in human body and need to be taken with diet or in the form of supplements³⁶. Lutein and zeaxanthin were also considered for inclusion in AREDS, but unfortunately, at the time of starting the study neither of them was commercially available.

Finally, the results of AREDS should encourage additional research into the mechanisms of retinal oxidative damage because a more substantial progress in the prevention and treatment of AMD will only be possible once the pathogenesis of the disease is fully explained.

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Sažetak

ULOGA VITAMINA U LIJEČENJU S DOBI POVEZANE DEGENERACIJE MAKULE

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Pregledno je prikazana uloga vitamina u liječenju s dobi povezane degeneracije makule. Za pregled su izabrane slijedeće studije: Eye Disease Case Control Study (EDCCS), Beaver Dam Eye Study, Blue Mountains Eye Study, Pathologies Oculaires Liees a l'Age Study (studija POLA) i Age Related Eye Disease Study (AREDS). Ove su studije pokazale kako se unos antioksidansa može preporučiti u bolesnika s određenim oblicima s dobi povezane degeneracije makule. Od budućih se studija očekuje konačan odgovor u svezi s ulogom antioksidansa.

Ključne riječi: *Degeneracija makule – etiologija; Degeneracija makule – prevencija i kontrola; Antioksidansi – metabolizam; Antioksidansi – primjena i doziranje; Prehrana*