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The role of B vitamins in the development and progression of age-related macular degeneration

The role of B vitamins in the development and progression of age-related macular degeneration

Małgorzata Figurska

Department of Ophthalmology, Military Institute of Medicine – National Research Institute in Warsaw
Head: Prof. Marek Rękas, MD, PhD

HIGHLIGHTS

A review of the current literature confirms the important beneficial role of B vitamins in limiting the development and progression of age-related macular degeneration.

ABSTRACT

In recent years, the importance of B vitamins as biologically active nutrients with potential effects preventing the development and progression of age-related macular degeneration has been analysed. This work is a review of the current literature from the last 10 years, dealing with the subject of the properties of B vitamins and research providing epidemiological data on its intake and plasma concentration and their impact on the disease in patients with macular degeneration.

The review confirms the important beneficial role of B vitamins in limiting the development and progression of macular degeneration. Although further randomized trials are needed to evaluate diet and determine selected plasma antioxidants over a longer, at least several years' period while taking into account a number of risk factors for modifiable and determine selected plasma antioxidants over a longer, at least several years' period while taking into account a number of risk factors for modifiable and non-modifiable macular degeneration.

Key words: age-related macular degeneration, risk factors, antioxidants, B vitamins, nutrition

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of central vision loss in developed countries [1]. The pathogenesis of the condition is complex and multifactorial. Non-modifiable risk factors for AMD are aging and increasing oxidative stress with age, genetic predisposition, female gender and light iris color. Modifiable factors are environmental in nature. Lifestyle (smoking, diet low in vitamins and micronutrients) predisposes to the development of AMD [2–4]. The condition is progressive, with advanced atrophic or neovascular changes leading to permanent significant visual impairment. Systematic evaluation of the ocular fundus in people over 40 and non-invasive, reproducible diagnostic tests, such as optical coherence tomography (OCT) of the macula, make it possible to detect the disease in the early stages of drusen and monitor its course [5]. Repeated therapy with intraocular vascular endothelial growth factor-blocking drugs used in wet AMD preserves useful visual function for a longer period of time [6].

From an epidemiological point of view, it is important to halt the progression of the disease to advanced AMD, thereby reducing the medical and social burden of chronic treatment and disability. Previous epidemiological studies have found that increased intake of antioxidants (vitamins, micronutrients) and lutein [7], omega-3 polyunsaturated fatty acids [8], and the use of a Mediterranean diet significantly reduces the risk of AMD progression [9]. Results from the Age-Related Eye Disease Study (AREDS) indicate that vitamins C, E, β-carotene combined with copper reduce the risk of progression to advanced AMD by 25% over a 5-year period [7]. Since β-carotene increases the risk of lung cancer in former smokers, lutein or zeaxanthin may replace it and provide the beneficial effects of the AREDS formula [10].

In recent years, the importance of B vitamins as biologically active nutrients with possible effects in preventing the development and progression of AMD has also been studied. The purpose of this paper is to review the literature from the last 10 years on the properties of B vitamins and studies providing epidemiological data on their intake and concentration, as well as their effect on the progression of degeneration in AMD patients.

PROPERTIES OF SELECTED B VITAMINS

Folic acid (folacin, vitamin B_9) is an organic chemical compound in the B vitamin group. The name comes from the Latin word folium meaning "leaf." In the human body, this substance is synthesized by intestinal bacteria, and its biologically active form is levomefolic acid (5-MTHF) [11]. Folic acid in food is found in the form of salt, or so-called folate. Therefore, the term vitamin B_9 often includes the entire group of these compounds. It is found in leafy vegetables, mainly spinach, but also in lettuce, cabbage, broccoli, asparagus, cauliflower, brussel sprouts, and in smaller amounts also in tomatoes, peas, beans, lentils, soybeans, beets, sunflowers, nuts, brewer's yeast, liver, egg yolk, wheat, oranges, bananas and avocados. The effects of folate deficiency in the body are: stunted growth and restoration of cells in the body, megaloblastic anemia, feelings of fatigue and trouble concentrating, anxiety, anxiety, depression, memory problems, disorders of digestion and nutrient absorption, diarrhea, decreased appetite, reduced body weight, inflammation of the tongue and lip mucosa, headaches, palpitations, premature graying of the hair, as well as stunted growth both in children and adolescents [12–14].

Pantothenic acid is sometimes mistakenly equated with vitamin B_5 [15]. In fact, vitamin B_5 is a mixture of: pantothenic acid, pantheine (a derivative of pantothenic acid), panthenol (belonging to the group of alcohols, not found in nature, but biologically active in humans and animals), coenzyme A (biologically active form of pantothenic acid). Pantothenic acid is essential for the proper metabolism of proteins, sugars and fats and for the synthesis of certain hormones, accelerates wound healing, determines the proper course of energy release, prevents fatigue, improves the cardiovascular, nervous and speech systems, participates in the production of fats, cholesterol, hormones and nerve transmitters, participates in tissue regeneration, improves pigmentation and hair condition [16]. Sources of vitamin B_5 include liver, wheat bran, fish (e.g., herring, mackerel, trout), mushrooms, whole milk, chicken meat, royal jelly, sunflower seeds, cheese, nuts, eggs, avocados, oranges, potatoes, broccoli, dark rice, melons, whole-grain bread, soybeans, peanut butter, bananas, yerba mate. The daily requirement for vitamin B_5 is about 7 mg.

Vitamin B_6 is a group of 6 organic chemical compounds, pyridine derivatives: pyridoxine, pyridoxal and pyridoxamine and their 5'-phosphates. The biologically active form is pyridoxal phosphate, other forms are converted enzymatically to it through the action of kinases and oxidases. Vitamin B_6 is soluble in water and is a precursor to important coenzymes that control the course of many key biochemical reactions. The most common cause of this vitamin deficiency is the use of isoniazid. Vitamin B_6 is involved in the metabolism of amino acids, facilitates their breakdown, the metabolism of fats and carbohydrates, enables energy storage, participates in the formation of enzymes, hormones, hemoglobin, the production of prostaglandins. It affects blood pressure, muscle contractions, heart function, proper functioning of the nervous system, and boosts immunity [17]. The richest sources of vitamin B_6 include chick peas, fish, meat, potatoes and other starchy vegetables, as well as some fruits (e.g. bananas). The adult daily requirement for vitamin B_6 is about 1–2 mg. In therapy the doses are much higher, in the range of 50–200 mg per day, or even 2–7 g.

Vitamin B_{12} (cobalamin) in living organisms plays a role as a regulator of erythrocyte production. Its deficiency causes anemia. Vitamin B_{12} is a very important coenzyme in methylation reactions in the body, including the methylation of homocysteine to methionine, catalyzed by methionine synthase. Vitamin B_{12} is also involved in the production of neurotransmitters, the formation of the myelin sheath of nerve cells. It affects the functioning of the nervous system. Vitamin B_{12} is mainly produced by bacteria living in the digestive tract of animals. In humans, it is formed in symbiosis with bacteria of the digestive system [18].

Vitamin B_{12} is mainly found in animal products. Its sources in the human diet include: meat products, fish, eggs, milk and milk products, mushrooms (e.g., oyster mushroom and champignon). The daily adult requirement for vitamin B_{12} is 2.4 μg. A healthy person stores about 3 mg of vitamin B_{12} in their body, which allows for several years of coverage, so its absence in the diet for a certain period of time is not dangerous to health. The serum concentration of vitamin B_{12} is 0.12–0.66 nmol/l, but in some liver diseases it increases significantly to 2–15 nmol/l [18].

B VITAMINS AND MACULAR DEGENERATIVE DISEASES

Low plasma concentrations of B vitamins can increase the risk of developing degenerative diseases such as dementia neurodegeneration or osteoporosis. It also contributes to the development of cardiovascular diseases. B vitamins play a key role in DNA methylation and synthesis, as well as DNA repair and replication [19]. Vitamin B_6, folic acid and vitamin B_{12} regulate homocysteine levels, and hyperhomocysteinemia is a potential risk factor for AMD. In contrast, reduced serum levels of B vitamins are characteristic of AMD. Gopinath et al. studied the relationship between plasma total homocysteine, vitamin B_{12} and folic acid levels and AMD over a 10-year period [20]. Increased plasma homocysteine levels were associated with an increased risk of AMD in general, including the early stage. Study participants with serum vitamin B_{12} deficiency (< 185 pmol/l) had a higher risk of early and late AMD. Folic acid deficiency (< 11 nmol/l) was associated with a 75% and 89% increased risk of incident early and any stage of AMD. Participants who reported additional vitamin B_{12} intake had a 47% lower risk of developing AMD in any form.

Huang et al. in 2015 assessed the links between the aforementioned compounds and AMD using data from PubMed, Medline and Embase databases [21]. In the end, the researchers analyzed 11 studies (total number of patients: 1072 with AMD and 1202 in the control group), evaluating plasma homocysteine levels. Three additional studies were analyzed (152 AMD cases, 98 in healthy control), containing data on plasma concentrations of folic acid and vitamin B_{12}. As a result, it was showed that plasma homocysteine levels were 2.67 μmol/l higher in AMD patients than in the control group. In contrast, vitamin B_{12} levels in AMD patients were 64.16 pg/ml lower than in the control group. Subgroup analysis showed that folic acid levels were 1.66 ng/ml lower for wet AMD. The researchers conclude and confirm that based on current data, homocysteine can be considered a risk factor for AMD.

Moreover, Pinna et al. in 2018 conducted a systematic review and meta-analysis of published data on the correlation between homocysteine and AMD, especially its wet form [22]. The analysis included data from a selection of 12 studies. All of the selected studies evaluated wet AMD, and 4 of them also evaluated dry AMD. In terms of wet AMD, the analysis included a total of 453 cases and 514 control patients without macular degeneration. The mean homocysteine concentration was 1.1 μmol/l higher for wet AMD. However, significant heterogeneity of the studies ($p < 0.001$) was considered as data imitation. In an analysis of age-homogeneous data (6 studies of patients with wet AMD – 214 cases, 274 patients in the control group), the mean homocysteine concentration was 0.58 μmol/l higher, but the result was not statistically significant ($p = 0.144$), due to the moderate heterogeneity of the study groups. The analysis results allowed the researchers to reaffirm and show that there is some evidence of an association between wet AMD and elevated homocysteine levels. However, conclusions are limited by the variation in methodology of the studies analyzed. Fully valuable results can be obtained after analyzing data from homogeneous study groups, in prospective and randomized observations.

Reports of elevated plasma homocysteine levels in AMD patients are not always fully confirmed. One example is the valuable prospective study by Christen et al. whose results were published in 2018 [23]. During a follow-up period averaging 11.2 years in a large cohort of potentially healthy male physicians, the researchers prospectively assessed plasma homocysteine levels, their dietary determinants and AMD risk. As a result, they observed the occurrence of 146 cases of AMD with significant visual impairment (20/30 or less). The control group was matched for age, smoking and time of blood draw. At the beginning of the study, the intake of B vitamins and related compounds of betaine and choline was assessed using a dietary questionnaire. AMD was not associated with plasma homocysteine levels ($p = 0.99$). However, the incidence of AMD was inversely related to total intake of folic acid ($p = 0.08$), vitamin B_6 from food ($p = 0.01$) and betaine ($p = 0.048$). Such prospective data does not directly support a major role for homocysteine in the development of AMD, but suggest a possible beneficial role for a higher intake of several nutrients involved in homocysteine metabolism.

In 2016, Merle et al. published the results of examining the relationship between dietary folic acid, B vitamins

and progression of macular degeneration to geographic atrophy (GA), taking into account a number of factors [24]. Of the 2,525 people (4,663 eyes) from the Age-Related Eye Disease Study, 405 (528 eyes) had progression of AMD to GA over 13 years. Patients with at least one eye free of advanced AMD at the start of the study were included in the analyses. The risk of progression to GA decreased significantly with increasing dietary intake of thiamine, riboflavin and folic acid, after adjusting for age, gender and total energy requirements. After adjusting for demographics, behavior and genetics, the trends remained statistically significant for folic acid ($p = 0.007$) and were borderline for thiamine ($p = 0.05$). Statistical significance was not reached with regard to riboflavin ($p = 0.20$). Folic acid was significantly associated with a lower risk of incident GA in patients homozygous for complement protein 3 ($p = 0.0005$). The study did not produce significant data on the association of folic acid or other B vitamins with neovascular AMD.

Gopinath et al. assessed the risk of developing advanced AMD according to diet [25]. Patients with late-stage AMD compared to controls had significantly lower intake of vitamin E (7.4 vs 9.8 mg/24 h; $p < 0.0001$), β-carotene (6232 vs 7738 µg/24 h; $p < 0.0001$), vitamin C (161 vs 184 mg/24 h; $p = 0.0002$) and folic acid (498.3 vs 602 µg/24 h; $p < 0.0001$). A significantly lower percentage of patients with late AMD consumed the recommended amounts of vegetables, compared to the control group: 52.9% vs 64.5% ($p = 0.0002$). This study confirmed the effect of diet, including the intake of B vitamins, on disease progression. The randomized study by Christen et al. provided particularly valuable data on the evaluation of daily supplementation with folic acid and vitamins B_6 and B_{12} in the context of AMD risk reduction [26]. The evaluation included 5442 women at least 40 years old with existing cardiovascular disease or several risk factors for cardiovascular disease. A total of 5205 of these women did not have a diagnosis of AMD at the start of the study and were included in this analysis. Participants were randomly assigned to a group receiving folic acid (2.5 mg/24 h), pyridoxine hydrochloride (50 mg/24 h) and cyanocobalamin (1 mg/24 h) or placebo. After an average of 7.3 years of treatment and follow-up, there were 55 cases of AMD in the combination treatment group and 82 in the placebo group ($p = 0.02$). AMD with significant visual impairment occurred in 26 cases in the combination treatment group and in 44 cases in the placebo group ($p = 0.03$). Such randomized data from a study involving a large cohort of women at high risk for cardiovascular disease indicate that daily supplementation with folic acid, pyridoxine and cyanocobalamin can reduce AMD risk by nearly 40%.

Results of the prospective Alienor Study published in 2022 are also noteworthy. It evaluated the relation between dietary provision and serum concentration of vitamins and the incidence of advanced AMD [27]. The study included a population-based cohort of 963 residents of Bordeaux, France, aged at least 73 at the start of the study (recruited in 2006–2008). Ophthalmic evaluation was performed every 2 years for a period of 8 years. The prevalence of AMD was assessed by fundus photography of the retina and OCT examination. Of the 861 participants, 93 developed AMD during a mean follow-up of 9.8 years. Participants with normal serum folic acid levels (≥ 10 nmol/l) had a significantly 51% lower risk of AMD ($p = 0.036$). Participants with higher intakes of vitamins B_5 and B_6 had a 28% lower risk of developing AMD ($p = 0.049$). Serum deficiencies were found in the following percentages of patients: 12.6% (< 20 nmol/l) for vitamin B_6, 7.6% (< 10 nmol/l) for folic acid and 0.2% (< 185 pmol/l) for vitamin B_{12}. Among participants who developed advanced AMD, 15.9% were folic acid deficient compared to 6.7% among participants who did not develop advanced AMD. This cohort study of older adults suggests a strong association between normal serum folic acid levels and high intake of vitamin B_5 and B_6 and a lower risk of developing advanced AMD. The Alienor Study confirms that a healthy diet rich in B vitamins can reduce the risk of vision loss due to AMD. Based on the results of the Alienor Study, a diet containing folic acid (leafy vegetables, fruits, whole grains), vitamin B_5 (meat products, bread, milk-based products, vegetables) and B_6 (liver, fish, leafy vegetables) can be recommended.

In addition, the Alienor Study evaluated the association of plasma lutein and zeaxanthin concentrations with the incidence of advanced AMD [28]. Concentrations of lutein and zeaxanthin were determined at the beginning of the study in blood samples using liquid chromatography. Of the 609 participants, 54 developed advanced AMD during a mean follow-up of 7.6 years. Participants with higher plasma lutein levels had a significantly lower (by nearly 37%) risk of advanced AMD ($p = 0.03$). No statistical significance was found for other carotenoids.

CONCLUSIONS

Data on the importance of antioxidant supplementation in reducing the risk of AMD development and progression continues to be updated. Pameijer et al. in 2022 conducted another systematic review of randomized and non-randomized studies on the relationship between nutrition, the presence of antioxidant vitamins and minerals in the diet, and supplementation with them and AMD [29]. Again, the researchers studied Cochrane Central, Medline, EMBASE databases and included studies published between January 2015 and May 2021. The analysis of data from 7 randomized and 13 non-randomized studies again confirmed that a high dietary intake of the nutrients β-carotene, lutein and zeaxanthin, copper, folic acid, magnesium, vitamin A,

niacin, vitamin B_6, vitamin C, docosahexaenoic acid and eicosapentaenoic acid (EPA) is associated with a lower risk of progression from early stages of AMD to late stages. The use of dietary supplements containing antioxidants and minerals and adherence to the Mediterranean diet, characterized by a high intake of vegetables, whole grains and nuts with a low intake of red meat, is associated with a reduced risk of progression from early to late AMD.

A review of the current literature confirms the important beneficial role of B vitamins in limiting the development and progression of AMD. Although it has been frequently addressed by researchers in the past two decades, the discussion on the topic is still ongoing. Further randomized trials are needed, focused on dietary assessment and determination of selected antioxidants in plasma over a longer period of at least several years while taking into account a range of modifiable and non-modifiable AMD risk factors.

CORRESPONDENCE
assist. prof. Małgorzata Figurska, MD, PhD
Department of Ophthalmology, Military Institute of Medicine – National Research Institute in Warsaw
04-141 Warszawa, ul. Szaserów 128
e-mail: mfigurska@wim.mil.pl

ORCID
Małgorzata Figurska – ID – http://orcid.org/0000-0002-6366-802X

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