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The Role of Dietary Supplementation in the Prevention of Macular Degeneration: An Analysis of the Efficacy of Vitamins and Antioxidants in Inhibiting the Progression of Macular Degeneration

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Abstract

Introduction: Age-related macular degeneration (AMD), one of the leading causes of vision loss among the elderly, poses a significant global health issue. This is a retinal condition that causes the loss of central vision. The demographic shift towards an aging population contributes to the increasing number of individuals affected by this condition, presenting a challenge to the medical and scientific community in developing effective prevention and treatment methods. In recent years, considerable attention has been given to the role of a proper diet and the supplementation of vitamins and antioxidants in inhibiting the progression of AMD.

Objective: To analyze the efficacy of dietary supplementation in the prevention of macular degeneration, with a particular focus on the role of vitamins and antioxidants in inhibiting disease progression.

Materials and Methods: A review of the literature and scientific studies available in medical information databases such as PubMed, CrossRef, and Google Scholar.

Conclusions: The analysis of scientific literature, including clinical studies, provides significant data on the impact of supplementation on age-related macular degeneration (AMD). The initial stages of the Age-Related Eye Disease Study (AREDS) demonstrated a substantial reduction in the risk of AMD progression due to vitamin supplementation, which led to modifications in the original supplement composition in AREDS2. These studies offer valuable insights into the role of vitamins and antioxidants in the prevention and inhibition of AMD progression. However, not all studies are conclusive, and further research is necessary to confirm their efficacy. Additionally, promising results have emerged regarding the benefits of lutein and zeaxanthin, as well as zinc supplementation, though further studies are required to

better understand their mechanisms of action and potential benefits for individuals affected by AMD.

Keywords: AMD, vitamins, antioxidants, supplementation, inhibition of progression, lutein, zeaxanthin

Introduction:

Age-related macular degeneration (AMD) affects up to 12.5% of individuals over the age of 60 and is the leading cause of blindness among the elderly in developed countries. According to statistics, approximately 200 million people worldwide suffer from AMD, and this number is expected to increase to 288 million by 2040. The aging global population, along with improved diagnostic methods, contributes to the rapid rise in the number of AMD cases. Given the increasing prevalence of AMD, there is growing interest in the role of vitamin and antioxidant supplementation in the prevention and inhibition of disease progression. Analyzing these substances is crucial for understanding their impact on ocular disease processes and for developing effective intervention strategies. The introduction of these studies could lead to better eye health protection and an improved quality of life for individuals affected by AMD. Not all studies are conclusive, and more time and research are needed to confidently determine the efficacy of vitamin and antioxidant supplementation in halting the progression of macular degeneration [1].

Studies (AREDS) and AREDS2:

Research conducted as part of the Age-Related Eye Disease Study (AREDS) and its continuation, AREDS2, is a key source of information regarding the impact of vitamin supplementation on the progression of age-related macular degeneration (AMD). AREDS2 was a multicenter clinical trial conducted by the National Eye Institute (NEI) aimed at a more detailed examination of the effect of vitamin supplementation on AMD progression and assessing the synergistic effects of various nutrients on retinal health. The initial phase of

AREDS demonstrated a significant reduction in the risk of advanced AMD progression due to a vitamin supplement containing vitamin C, vitamin E, beta-carotene, zinc, and copper. However, due to advances in AMD knowledge and concerns about the potential side effects of some supplement components, AREDS2 introduced certain modifications to the original supplement formulation.

In the context of studying the effect of vitamin and antioxidant supplementation on inhibiting AMD progression, it is crucial to fully understand the nutrients involved and their mechanisms of action. AREDS2, with its comprehensive design and multicenter structure, provided significant data that may contribute to a more precise determination of the impact of supplementation on AMD progression [2].

AMD

AMD is a disease associated with the degeneration of the critical area of the retina called the macula. This area is the central point that collects the most light, as it contains the highest density of light-sensitive cells called cones. The macula plays a crucial role in providing sharp vision, recognizing fine details, and image resolution. The retina consists of two main layers: the inner neurosensory retina and the outer layer of retinal pigment epithelium (RPE) cells. The RPE layer is separated from the outer choroid by Bruch's membrane (BM), which is a modified basement membrane. The choroid consists of the choriocapillaris layer (an inner network of capillaries) adjacent to Bruch's membrane and an outer, more extensive layer of vessels. Its main function is to supply the retina, especially the macula, with oxygen and nutrients and to remove waste products from it [3].

Risk Factors and Causes:

Age is a significant risk factor for age-related macular degeneration (AMD), with approximately 10% of individuals aged 66 to 74 showing signs of the disease, a figure that increases to 30% in the 75-85 age group. Additionally, family history plays a crucial role, with the risk of developing AMD reaching 50% for individuals with a relative affected by the disease compared to 12% for those without a family history. Genetic factors also play a role, with

changes in genes related to the complement system identified as possible risk factors in AMD. Furthermore, arterial hypertension and elevated cholesterol levels are associated with an increased risk of AMD, while obesity, especially in men, constitutes another significant risk factor. There is also conflicting evidence regarding the impact of sunlight exposure, especially blue light, on the risk of AMD. Finally, cigarette smoking is strongly associated with the development of AMD, with tobacco smokers having 2-3 times higher risk of developing the disease compared to non-smokers. These risk factors are essential for understanding the etiology of AMD and may be key to developing preventive and interventional strategies in combating this disease [4].

Patomechanism:

The aging process of the eye involves the accumulation of unremoved cellular waste originating from the retinal pigment epithelium (RPE), which accumulates in the areas of contact between the RPE and Bruch's membrane and the neurosensory retina. These accumulations, called drusen, often constitute the first noticeable sign of AMD on ophthalmoscopic examination, appearing before noticeable deterioration in visual function. Drusen are complex structures, primarily composed of lipids but also containing proteins and carbohydrates, manifesting as small, white or yellow deposits on the macula. The accumulation of drusen in Bruch's membrane, along with other structural and biochemical changes associated with AMD pathogenesis (including sustained complement cascade activation and inflammation), leads to thickening and reduced permeability of the membrane [5]. This, in turn, hinders the transport of nutrients to the retina and the exchange of waste with the choroid, resulting in choroidal vessel thinning. These stages, combined with neurodegenerative changes in the photoreceptor-RPE complex, lead to RPE pigmentation aberrations, such as hypo- or hyperpigmentation, in the early or intermediate stages of the disease. This combination of factors impairs RPE and photoreceptor function [6].

Vitamin B:

A protective mechanism through which adequate intake of folic acid and vitamins B6 and B12 may influence the reduction of AMD-related risk could be the modulation of homocysteine

levels in the serum. Homocysteine is a product of amino acid metabolism, and its concentration increases in the case of deficiency of vitamin cofactors for enzymes catalyzing intracellular reactions. High homocysteine levels have been independently correlated with the risk of neurodegenerative and cardiovascular diseases, as well as AMD associated with them [7]. However, this relationship appears to be complex, as suggested by meta-analysis, limiting this association only to neovascular AMD [8]. This complexity may be due to the variable availability of the three B-group vitamin cofactors, other B-group vitamins, or common genetic variants influencing the activity of methylenetetrahydrofolate reductase, a key enzyme converting homocysteine to methionine [9].

Previous reports indicated a protective association between folic acid intake and the progression to geographic atrophy (GA) advanced AMD, but not neovascular AMD [10]. The results of current analyses are consistent between the AREDS and AREDS2 studies, further confirming this effect. Indeed, these results expand current knowledge by indicating a reduced risk of developing large drusen. However, in these studies, the associations of folic acid cannot be clearly separated from the effects of other B-group vitamins and minerals such as iron, magnesium, and zinc, given their high correlation in consumption. This is likely due to the common presence of these components in fortified breakfast cereals and leafy vegetables [2].

Vitamins E, A, C:

Clinical studies on the influence of vitamins on AMD, especially vitamins A, C, and E, provide conflicting results. Data from the National Health and Nutrition Examination Survey showed that high consumption of vitamin A-rich fruits and vegetables reduces the risk of AMD [11]. High dietary intake of vitamin C, despite its strong antioxidant activity, did not show an association with reduced risk of macular degeneration. In a clinical-control study conducted in the USA in 1994, there was no statistically significant reduction in AMD risk among individuals consuming large amounts of preformed vitamin A (retinol), vitamin E, or vitamin C [12]. These results were later confirmed in the AREDS study. Vitamin A plays a significant role in the phototransduction pathway. Despite this crucial function in the process, no

association was found between vitamin A intake and the risk of AMD (both early and neovascular) in numerous studies, including BMES, NHS+HPFS, and AREDS [13].

Additionally, data from the AREDS study showed that supplementation containing not only vitamin C and vitamin E but also beta-carotene and zinc reduced the five-year risk of developing AMD by 25% in at-risk patients. This effect persisted for five years after the end of the clinical trial. Post hoc analysis of AREDS and AREDS2 cohorts demonstrated a reduction in the risk of late AMD and geographic atrophy (GA) associated with vitamin A and C. Vitamin A was also associated with a reduced risk of nAMD. A population-based study on AMD risk factors showed that vitamin E, but not vitamin A and C, may protect against AMD. In contrast, a study on 1193 healthy women found that daily intake of vitamin E at a dose of 500 IU did not prevent the development or progression of AMD. Another study showed that dietary intake of vitamins E and C was associated with a reduced risk of nAMD in older patients in Japan. Dietary intake of vitamin A showed no correlation with nAMD risk.

In the Cochrane systematic reviews database, it was found that supplementation with vitamin C or vitamin E had little or no impact on the risk of developing any form of AMD, which was confirmed with high certainty, consistent with another meta-analysis. The role of vitamins in preventing AMD needs to be further investigated [14].

Vitamin D:

As part of the VITAL study, participants were randomly assigned to receive either vitamin D supplementation, omega-3 fatty acid supplementation, or a placebo. An additional investigation examined whether supplementation of these substances affected the risk of AMD. Analysis of the results showed that neither vitamin D supplementation nor omega-3 fatty acid supplementation had a significant impact on the risk of developing AMD among participants in the VITAL study. These findings suggest no benefit associated with vitamin D supplementation or omega-3 fatty acids in the context of AMD prevention [15].

The association between vitamin D and age-related macular degeneration (AMD) was also investigated based on data from the Third National Health and Nutrition Examination Survey (NHANES III) from 1988 to 1994 [16]. This study was part of the Centers for Disease Control and Prevention (CDC) efforts to understand AMD risk factors. The results of the NHANES III data analysis indicated that regular use of supplements containing vitamin D was not generally associated with the occurrence of early AMD in the studied population.

However, an interesting association emerged in the subgroup of individuals consuming less than one serving of milk per day. In this subgroup, individuals who regularly used supplements containing vitamin D were observed to have a reduced risk of early AMD. This finding suggests that vitamin D intake may have a beneficial effect on AMD risk among individuals with lower milk consumption. Although not statistically significant, this result provides an interesting clue for further research on the impact of vitamin D on AMD development. This conclusion may be significant for clinical practice, emphasizing the potential role of vitamin D supplementation in AMD prevention [17].

Lutein and Zeaxanthin:

Age-related macular degeneration (AMD) correlates with a deficiency of macular carotenoids in the retina of the eye. Among many carotenoids, only lutein and zeaxanthin are accumulated in the human eye retina. Other carotenoids from the blood serum, of which there are over twenty, do not exhibit such selective accumulation in the retina [18].

Studies on the influence of lutein and zeaxanthin on the inhibition of macular degeneration (AMD) have shown consistent relationships between higher consumption of these carotenoids and reduced frequency of late-stage AMD. A meta-analysis conducted in 2012 confirmed that high consumption of lutein/zeaxanthin was associated with a lower risk of late-stage AMD [19]. Similar results were observed in a cohort study conducted among US healthcare workers, where high consumption of lutein/zeaxanthin was associated with a reduced risk of late-stage AMD, mainly representing the neovascular form of AMD [20]. These results are consistent with the findings of the current study, suggesting a correlation between lutein/zeaxanthin

consumption and AMD risk reduction. Additionally, other studies have shown a similar pattern of results for other carotenoids, such as β-cryptoxanthin, α-carotene, and β-carotene.

There is also high-quality evidence confirming the efficacy of lutein/zeaxanthin, as demonstrated in the AREDS2 randomized controlled trial (RCT). Adding lutein and zeaxanthin to the original AREDS formulation resulted in a significant reduction in the risk of progression to advanced AMD [2]. Lutein, both alone and in combination with zeaxanthin, demonstrates the ability to improve other aspects of visual function, such as multifocal electroretinography (ERG) outcomes and contrast sensitivity, which are alternative indicators of visual quality. Studies on the impact of lutein and zeaxanthin on age-related macular degeneration (AMD) indicate their potential benefits.

For instance, a study on zeaxanthin and visual function showed that using zeaxanthin alone provided greater benefits in terms of high contrast sensitivity and shape discrimination, while lutein alone provided greater benefits in terms of low contrast sensitivity. These results confirm that lutein and zeaxanthin may be effective factors in inhibiting the progression of macular degeneration.

The consumption of other carotenoids, such as cryptoxanthin and lycopene, has also been studied. Overall, no association has been found with either increased or decreased risk associated with age-related macular degeneration (AMD). Therefore, while consuming green vegetables may protect against the development and progression of AMD, this effect cannot be unequivocally attributed to increased consumption of specific green vegetable components. It is generally recommended to consume at least 2-4 servings of leafy green vegetables per week to benefit from the carotenoid content in the diet. Additional benefits can be obtained by regularly consuming up to 2 servings per day, especially when combined with other healthy habits such as avoiding tobacco smoking [13].

Zinc:

Zinc is a micronutrient that serves as a cofactor for many enzymes, also characterized by its antioxidant properties. In biochemical mechanisms, zinc inhibits the production of reactive oxygen species (ROS) by suppressing the activity of NADPH oxidase, responsible for generating superoxide anion (O2•−). Additionally, zinc is a significant component of superoxide dismutase (SOD), an antioxidant enzyme, and an inducer of metallothionein, a protein involved in the removal of hydroxyl radicals (HO•) [21]. It enhances the expression of genes encoding antioxidant enzymes such as heme oxygenase 1, glutathione, glutathione S-transferase, and superoxide dismutase, positively regulating the nuclear factor erythroid 2-related factor 2 (Nrf2), which is activated by zinc [22]. All types of cells in the human eye retina contain zinc ions.

Preclinical studies conducted on cell cultures have shown that zinc, in a dose-dependent manner, increases glutathione production in human retinal pigment epithelial cell cultures (ARPE-19), activating the Nrf2 pathway [23]. Furthermore, zinc induced the synthesis of the antioxidant metallothionein, protecting lipid membranes from peroxidation. Observations on Brown Norwegian rats fed a zinc-deficient diet showed the development of metallothionein deficiency and increased lipid peroxidation in the retina. In an animal model of light-induced retinal degeneration in Sprague-Dawley rats, intraperitoneal zinc administration protected retinal cells from damage, and a synergistic effect was observed with a combination of zinc and rosemary extract (Rosmarinus officinalis).

The role of zinc supplementation in AMD has been confirmed in many clinical studies. The first of these, conducted by Newsome et al. on a group of 151 patients with AMD or retinal drusen presence, showed a significant reduction in vision loss in the supplementation group compared to the placebo group after 12 to 24 months of observation. The Age-Related Eye Disease Study (AREDS), involving 3640 participants, confirmed that zinc supplementation alone reduces the risk of AMD progression. Additionally, it was observed that zinc supplementation along with an additional antioxidant significantly reduces the decline in visual acuity, which is significant in AMD. The results of other studies, such as the Rotterdam Study, the Blue Mountains Eye Study, and the Beaver Dam Eye Study, also confirmed the beneficial

effect of zinc supplementation in reducing the severity of AMD, especially in the early stages of the disease [14].

Discussion

Research on the impact of vitamins and antioxidants is a significant contribution to understanding this disease, which poses a major health problem, especially in aging communities. With the growing number of AMD cases, research is increasingly focusing on ways to prevent this disease.

Analysis of scientific literature, including clinical studies such as the Age-Related Eye Disease Study (AREDS) and its follow-up AREDS2, provides important data on the impact of supplementation on AMD. The initial stages of AREDS showed a significant reduction in the risk of AMD progression through vitamin supplementation, leading to modifications of the original supplement composition in AREDS2. These studies provide insight into the mechanisms of supplement action and confirm their beneficial effect on reducing AMD risk.

Conducting research is crucial for understanding the etiology of this disease and for developing preventive and interventional strategies. Research on the role of individual nutrients, such as vitamins A, C, E, B, D, zinc, lutein, and zeaxanthin, yields diverse results, highlighting the complexity of mechanisms associated with AMD. There are inconsistencies in the results regarding the effectiveness of individual components, suggesting the need for further research in this field.

The conclusions from conducted studies indicate the potential benefit of vitamin and antioxidant supplementation in the prevention and inhibition of AMD progression. However, further research is necessary to better understand the mechanisms of action of individual components and their synergistic effects. Developing more precise interventional strategies may contribute to better eye health protection and improve the quality of life for individuals affected by AMD.

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