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Vitamin E and Supplements Offer Eye Neuroprotection – Myth or Reality?

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Background: Several studies suggested that nutrition might have an effect on eye health. Although exposure to nutrients is ubiquitous, on the other hand without it, we generally cannot survive and an exposure too high or too low causes health problems. Vitamins are a good example and the ubiquitous exposure to vitamins has led to many epidemiological studies for many diseases, including glaucoma.

Abstract: Leading causes of vision loss include several eye conditions such as cataract and glaucoma. The role of nutritional supplementation to prevent the progression of ocular disease is of great interest to health care professionals. It is recognized that the crystalline lens and retina suffer oxidative damage and the most protective agents are anti-oxidant vitamins A, C and E. The Age-Related Eye Disease Study (AREDS), found that supplementation with vitamins C and E, reduced the risk of developing various ocular diseases. The RDA for vitamin E is 15 mg/day α-tocopherol for both women and men. Vitamin E exists naturally in nuts and seeds, in addition to dark leafy vegetables. In a recent study reported lower plasma levels of vitamin E in POAG subjects.

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Conclusion: In conclusion, exposure to nutrients although is ubiquitous, without it, in general we cannot survive. Conflicting evidence is presented for vitamins A and E in prevention of ocular disease. A number of epidemiological studies showed an increased risk of nuclear or cortical cataract in people with low blood levels of vitamin E. Furthermore, a number of studies suggested that nutrition might have an effect on the intraocular pressure (IOP) or glaucoma, arbitrated by oxidative stress.

Keywords: Glaucoma; vitamin E; antioxidant supplements; crystalline lens; oxidative stress; cataract.

1. INTRODUCTION

Several recent studies, reported that vitamins and supplements directly affect the eyes or support the physical health, upon which the eye depends. Vitamins today are also often referred as micronutrients [1]. It is also widely known that the crystalline lens and retina undergo oxidative damage. It is also believed that the antioxidant vitamins A, C and E are protective factors for the eye. Also current research has revealed that approximately 250 million people worldwide suffer from varying degrees of vision problems [2]. The main causes are due to eye diseases, such as cataract, AMD, glaucoma and diabetic retinopathy. On the other hand, up to date studies have given controversial results on the role of nutrition in cataract development [3]

Furthermore, a variety of epidemiological studies, bitterly support the view that diet plays a vital role in the development of cataract in human eyes. In some regions of the world, cataract occurs more frequently in people of low socioeconomic status, low health care, and low education [4,5]. In this case, the role of dietary supplements to prevent eye disease progression, is of particular interest for eye health professionals and patients.

"Vitamins A, B, C and E are above all motivating. Of course, the evidence for vitamins A and E in the prevention of eye disease is rather contradictory. These vitamins are involved in the production of rhodopsin but also in the prevention of lipid peroxidation. In patients with age-related macular disease, significant improvements have been noted with the use of lutein and zeaxanthin supplements" [6].

"The US National Eye Institute study, recognized as the Age-related Eye Disease Study (AREDS), found that supplementation with vitamins C and E, β-carotene, zinc and copper (Table 1) at levels well above the recommended daily dose, reduces the risk of advanced AMD developing, by approximately 25%" [7].

Table 1. Nutrition content of the Age-Related Eye Disease Study (AREDS) formulation (after Rasmussen and Johnson, 2013)

Nutrient	Daily dosage	% Daily value
Vitamin C (ascorbic acid)	452mg	754
Vitamin E (DL-α-tocopheryl acetate)	400IU	1334
Zinc (zinc oxide)	69.6mg	464
Copper (cupric oxide)	1.6mg	80
Vitamin A (β-carotene)	$28{,}640\text{lU}(17\text{mg})$	572

1.1 Vitamin E

Eight distinct fat-soluble compounds of tocopherols and tocotrienols emerge in nature, for Vitamin E, with each subgroup having α, β, γ, and δ subtypes. Seeds like sunflower, and nuts, for example almonds and hazelnuts are rich sources of vitamin E, as well as dark leafy vegetables such as spinach and collard greens.

"Vitamin E is a fat-soluble antioxidant that reacts with oxygen preventing the oxidation of fatty acids. The retina is a lipid-rich environment and is exposed to UV radiation. In a study concerning cell culture, vitamin E has been found to enhance the antioxidant capacity of lutein to protect retinal melanocytic epithelial cells from acrolein-induced oxidation" [8]. "After the neutralization of a free radical, by a molecule of α-tocopherol, its antioxidant capacity is completely lost. Then other antioxidants, like vitamin C, are able to regenerate the antioxidant capacity of α-tocopherol" [9].

"α-Tocopherol is a form of vitamin E that is actively maintained in the human body as well as in blood and tissues" [1]. "In addition, the chemical form meets the RDA for vitamin E. The primary function of α-tocopherol is antioxidation. In contrast, fats are prone to destruction by free

radicals, through oxidation. Therefore α-tocopherol attacks free radicals one by one to prevent lipid oxidation. Since the retina contains a high concentration of fatty acids, the above process seems to be very important" [10].

The recommended intake dose of vitamin E is 22.4 IU, [11,12] while the dose used in AREDS2 was 400 IU daily. "One ounce of sunflower seeds meets the daily RDI, although the dose used in AREDS2 are 18 times higher than required. Other functions of α-tocopherol potentially beneficial to eye health include effects on the behavior and activities of molecules and enzymes in cells of the immune system. In addition, α-tocopherol has been shown to inhibit platelet aggregation and improve vasodilation" [13].

"The RDA for vitamin E is 15 mg/day of α-tocopherol for both women and men (≥19 years)" [13]. "The average intake of vitamin E from food in the US for men and women over age 50 is 8.6 and 7.3 mg/day, respectively. Foods rich in vitamin E and some recommended serving sizes are shown in Table 2" [11].

1.2 Vitamins and Glaucoma

"A number of studies have shown that diet may affect eye health. Although nutrient exposure is ubiquitous, without it, we generally unfortunately cannot survive, and extremely high or very low an exposure may cause health problems. Vitamins are a good example, and ever-present exposure to vitamins has led to many epidemiological studies of many diseases, including glaucoma" [14].

"Glaucoma is a disease including groups of optic neuropathies that lead to progressive retinal ganglion cell death, optic nerve degeneration, and eventually typical changes such as visual field defects" [15,16]. "Primary open-angle glaucoma (POAG) is the most common type and is different from normal-tension glaucoma (NTG) specified that in the previous, IOP is often elevated" [15,17]. In case that glaucoma remains uncontrolled, then visual consequences are irreversibly [18,19,20]. present treatment includes topical ocular hypotensives as first-line treatment [18].

"Today, aging and high intraocular pressure (IOP) are still the most significant risk factors for the development of glaucoma. The need to study glaucoma in relation to vitamins stems from the observation that glaucoma is the leading cause of irreversible blindness. Additionally, nearly half of glaucoma cases are undiagnosed, and consequently the prevalence increases over time" [21,22].

"Another major risk factor for glaucoma, is considered the elevated intraocular pressure (IOP). Despite useful IOP-lowering therapies, disease progression is considerable for a number of patients. Oxidative stress occurs when more reactive oxygen groups are formed than the cell's antioxidant capacity. This leads to damage of the aqueous humor outflow system of the eye and the trabecular meshwork, resulting in an increase in IOP and ultimately retinal ganglion cell death" [23, 24].

As a result, alternative strategies aimed primarily to delay RGC degeneration, are used as the current course of therapy for glaucoma [25]. All the same, lowering IOP with suppressive medicines or other surgical procedures remains the only available treatment, at present [26].

Table 2. Vitamin E content of foods (after Rasmussen and Johnson, 2013)

Food	Serving	Milligrams (α-tocopherol equivalents)
Almonds, slivered	1/4 cup (27 g)	7
Corn oil	1tb(14 g)	2
Peanuts	1/4cup (37 g)	3
Peanut butter, smooth	2 tb (32 g)	3
Sunflower seeds	1/4 cup (35 g)	12
Safflower oil	1tb(14 g)	5
Soybean oil	1tb(14 g)	1
Wheat-germ oil	1tb(14 g)	20

Note:"Edible portion
Abbreviation: tb, tablespoon

RGC death is the result of several mechanisms, including trophic factor deprivation [27], inflammation [28], oxidative stress [29], mitochondrial dysfunction [30], excitotoxicity [31], dysregulation of autophagy [32], protein misfolding [33], ischemia and hypoxia [34]. Each of these methods may support disease etiology and progression and is a future target for novel neuroprotective management, but IOP-independent. Importantly, the actions of prolonged oxidative stress should be considered as a key factor [28,29,35].

“Retina is particularly vulnerable to oxidative stress due to its high oxygen consumption and polyunsaturated fatty acid ratio and direct exposure to light” [36]. This vulnerability increases with aging, due to the physiological decline of antioxidant defense mechanisms [36]. “In the aqueous humor of patients with primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) have been found high levels of oxidative stress markers” [37, 38].

In a previous study, Zanon-Moreno and colleagues (2013) reported lower plasma vitamin E levels in subjects with POAG [39]. Conversely, some studies have shown an increase in serum vitamin E levels in glaucoma patients [40]. Two studies in NTG patients showed no difference in plasma vitamin E levels between glaucoma patients and controls [41,42] and conversely, Lopez-Riquelme et al (2015) reported lower plasma vitamin E levels in NTG patients [43].

1.3 Nutrition and Cataract

“Age-related cataract is the leading cause of blindness in the world. The prevalence and impact of age-related cataracts is increasing dramatically as the proportion of seniors in world’s population continues to grow. Diabetic cataract is caused by an increase in polyols within the lens of the eye, catalyzed by the enzyme aldose reductase. Statistics estimate that more than 68% of people aged 79 years and older may have some degree of lens opacities or cataracts” [44].

“The cataract formation mechanism involves the poor level of glutathione adding to a dysfunctional antioxidant defense system within the crystalline lens of the eye. Nutrients that may enhance glutathione level and activity include lipoic acid, vitamins E and C, and selenium” [45]. “Aging, the greatly organized crystalline fibers of the clear crystalline lens are thought to dehydrate and photooxidize, leading to cross-linking and aggregation. Because oxidative damage is hypothesized to be fundamental to cataract development, many studies are required to investigate any protective effect of oral antioxidant supplementation” [46].

“The cataract analysis of the AREDS trial showed no difference between the intervention and placebo groups regarding the development or progression of age-related cataract or visual acuity loss” [47]. “Contrary to the Linxian study, AREDS participants were principally white (96%) and well-nourished. The study's primary outcomes were initially the progression of lens opacity or cataract surgery and additionally loss of visual acuity, measured by the loss of 15 or more letters in one eye over time. The probability of a lens-related event was estimated to be 30% over 5 years in all subjects despite the effects of the intervention” [47].

Observational studies results indicate that healthy lifestyle, with a diet containing foods rich in antioxidants, particularly lutein and zeaxanthin, as well as n−3 fatty acids, appears likely to be beneficial for cataract. Regarding the relationship between cataract and supplementation, a few randomized trials were originally designed to assess cataract (2 of them were in China) [47, 48,49], and 2 other studies assessed cataract later in clinical trials designed for other diseases [50, 51]. “A multivitamin-polymineral supplement with a combination of vitamin C, vitamin E, beta-carotene and zinc (with copper oxide) may be recommended for AMD but not for cataract” [52].

“Although the pathogenesis of age-related cortical and nuclear cataracts is different, oxidative damage has been implicated as an underlying cause of the distinctly different damage phenotypes” [53,54,55,56,57]. “Because of this relationship between oxidative stress and cataract formation, it has been suggested that topical application and dietary interventions with antioxidants can be used as treatments to delay or prevent cataract progression” [53,54,55,56,57]. Other nutrients and botanicals that may prevent or help prevent cataracts include panthetin, folic acid, melatonin, and bilberry.

“On the other hand, a number of epidemiological studies have shown an increased risk of nuclear or cortical cataract in people with low blood vitamin E levels [58,59]. Vitamin E deficiency can

lead to the formation of toxic peroxides and melanodialdehydes due to the general acceleration of tissue oxidation resulting in lens opacification. Unfortunately, a simplistic view of supplementing the lens with antioxidants has been shown to be ineffective and in some cases harmful in delaying cataract progression" [53].

The dietary amount of vitamin E supplementation clearly affects the change in protein structure accompanied by a change in glutathione level in the lens. This elevation may effectively protect the lens membrane from lipid peroxidation, which in turn probably reduces the risk of protein oxidation. Therefore, adequate antioxidant supplementation such as vitamin E may protect lens proteins from oxidative abuse. Conversely, excessive intake of vitamin E can reduce its inherent antioxidant benefit

2. RESULTS AND DISCUSSION

In summary, there seems to be a general consensus that a diet rich in fruits and vegetables containing vitamin C, E, A (Table 3) and multivitamin mineral supplements may be protective against cataract. Data on supplemental antioxidants provided as low-dose multivitamins appear generally positive, whereas results obtained using single nutrient antioxidants ranged from moderately effective to possibly harmful. Based on current data, a healthy diet and a multivitamin supplement may offer protection against cataract. If this is the case, it is important to consider how these nutrients can reach the lens in sufficient quantities to be effective in protection from oxidative damage.

Table 3. Main sources of vitamins (After Harvard Health Publishing, Harvard Medical School, 2021)

Vitamins	Sources
Vitamin C (L-ascorbic acid)	Citrus fruit, potatoes, broccoli, bell peppers, spinach, strawberries, tomatoes, Brussels sprouts
Vitamin D (cholecalciferol)	Fortified milk and cereals, fatty fish
Vitamin E (tocoferol)	Vegetables oils, leafy green vegetables, whole grains, nuts

"In general, many studies support that vitamin E is an essential antioxidant. Six studies reported a possible association between vitamin E blood levels and glaucoma. One of these studies reported lower plasma vitamin E levels in the POAG group" [43]. One study reported no association [60] and two other studies found elevated serum vitamin E levels in glaucoma patients.

For normal-tension glaucoma (NTG), one study showed lower plasma vitamin E levels in NTG patients [60], while other studies found no difference in plasma vitamin E levels between NTG patients and controls [60,61,62]. "Regarding the aqueous humor, lower levels of vitamin E have been reported in patients with POAG and PACG" [63]. On the other hand, studies on dietary vitamin E intake and its association with OAG reported no significant relationship [60].

"In conclusion, exposure to nutrients although ubiquitous, without it we generally cannot survive and exposure to excessively high or very low amounts causes health problems. Vitamins are a good example and the everywhere experience of the action of vitamins has led to many epidemiological studies on many diseases and glaucoma" [22]. In addition, a number of studies suggest that diet may have an effect on intraocular pressure (IOP) or glaucoma, which is mediated by oxidative stress.

3. CONCLUSIONS AND FUTURE STRATEGIES

The basic principle of using dietary supplements in glaucoma is sustained by a significant amount of literature demonstrating that the natural compound enriched with antioxidant, anti-inflammatory and anti-apoptotic activities is quite successful in preventing RGC death in models of retinal degeneration. On the other hand, the clinical significance of these data has yet to be demonstrated. Indeed, in a significant number of clinical studies, the small number of patients included, the heterogeneity of the study design, and the short follow-up period make it difficult to derive the clinical benefit of the treatment. Furthermore, extra vigilance is required when interpreting the results. However, although advance research is needed to establish their effectiveness and safety, dietary supplements may be helpful in the treatment of glaucoma.

The world's population is aging and as a result age-related cataracts have grown to epidemic proportions, placing severe pressure on global and local health systems. Since the onset of lens cataract is closely related to oxidative damage, the use of exogenous antioxidant interventions

has been promoted as a technique to maintain the slow progression of lens cataract. However, the majority of these studies are unsuccessful in slowing the progression of cataract.

Almost none of the described medical prevention studies showed convincing success. The main flow of results suggests that the protective effect of antioxidant vitamins identified in previous case-control and epidemiological studies, may have been perplexed by other lifestyle factors [64]. People who are regular users of multivitamins are more likely to be health conscious. Further randomized clinical trials and meta-analysis of data from previous randomized trials will be required to determine whether cataracts could be prevented or delayed with the use of vitamin supplements of any type. Although oxidation and inflammation are highly implicated in the etiology of these age-related eye diseases, a recent survey of middle-aged patients found that more than half of respondents were unaware of important nutrients that play a key role in health of the eyes.

The authors believe that awareness of nutritional information among young and middle-aged patients about natural vitamins in the diet is of great importance. Additionally, supplements may offer an alternative to natural vitamins, but more investigation is needed about their effectiveness and safety.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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