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COMMENT

Could the AREDS formula benefit patients with glaucoma?

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Eye (2022) 36:918–920; https://doi.org/10.1038/s41433-022-01956-0

Nutritional factors are hypothesized to be linked to the development of several eye diseases, as antioxidants may protect retinal ganglion cells (RGCs) from oxidative stress, which can damage cellular macromolecules and organelles. While the Age-Related Eye Disease Study (AREDS) trial provided evidence suggesting that nutrition could play a role in preventing advanced age-related macular degeneration (AMD) progression, there is limited research correlating dietary supplements with glaucoma prognosis, and the exact mechanism through which antioxidants may impact glaucoma prevalence is not well understood. Many questions have arisen regarding this topic, including whether the AREDS formula benefits glaucoma patients and how lessons learned from AREDS could help with designing a similar clinical trial for glaucoma.

The AREDS formula is commercially available and recommended for patients at high risk of developing advanced AMD. AREDS was a randomized clinical trial that investigated the efficacy of high-dose antioxidants and mineral supplements for AMD and age-related cataracts. The AREDS formula includes 500 mg vitamin C, 400 units vitamin E, 15 mg beta-carotene, 80 mg zinc, and 2 mg copper. A statistically significant benefit was observed for the combination of high-dose antioxidants and zinc in patients at high risk of developing advanced AMD, providing a 34% reduction in risk over a median of 6.3 years [1]. There was no benefit observed for patients with no or early AMD. The AREDS2 trial tested the same formula from the AREDS trial, substituting 10 mg lutein (L) and 2 mg zeaxanthin (Z) for 15 mg beta-carotene and reducing the concentration of zinc, on patients with bilateral large drusen or large drusen in one eye and advanced AMD in the other eye who were at risk of progression to advanced AMD. Changes in the AREDS2 formulation did not reduce development of AMD or alter visual acuity [2]. Since there is a potentially higher incidence of lung cancer in present and former smokers taking beta carotene supplements, the AREDS2 trial has suggested that L/Z could be a safer substitute to beta-carotene in the AREDS formulation [3].

Glaucoma is an optic neuropathy in which RGCs degenerate over time, resulting in irreversible visual sensitivity loss and blindness. The disease can remain asymptomatic until patients are in an advanced stage and affects more than 70 million individuals worldwide [4]. Several theories describe the pathophysiology of glaucoma. The mechanical theory suggests that damage due to increased intraocular pressure (IOP) occurs to the lamina cribrosa, while the vascular theory posits that ischemia or decreased perfusion of the optic nerve results in neurodegeneration [4]. Other theories on the pathophysiology of glaucoma include abnormal immunity and dysfunctional supporting tissues such as glial cells, which trigger oxidative stress and can further damage RGCs [4]. The risk of glaucoma increases with age, as changes in vasculature, collagen fibre stiffness, and immunity result in an optic nerve susceptible to damage. Therefore, it is necessary to monitor IOP among patients and protect RGCs to effectively treat glaucoma.

Could a high-dose antioxidant in the AREDS formula benefit glaucoma patients? The answer to the question is complex. Our analysis demonstrated that the AREDS formula had a neutral effect on IOP in patients without glaucoma; the effects of the AREDS formula on patients with glaucoma is unknown [5]. It is also plausible that the potential effects of the AREDS formula are independent of IOP. Table 1 summarizes the effect of each ingredient in the AREDS and AREDS2 formulas on development of primary open-angle glaucoma (POAG) [6–21]. Some studies suggest that the ingredients in the AREDS formula are beneficial for POAG, but results are mixed. For example, Coleman et al. demonstrated that the prevalence of POAG, as detected by visual field testing and optic disc examination, was reduced among women aged 65 years old and older with a history of osteoporosis or bilateral hip replacement who consumed carrots (vitamin A and carotenes), green collards and kale (vitamins A, C, B2, and B-carotene), and peaches (vitamin A), although the significance varied based on servings consumed per month [22]. The results from Coleman et al. are encouraging; however, epidemiological studies do not universally agree on the relationship between dietary antioxidants and the prevalence of glaucoma [10, 14]. The discrepancy is likely due to the variation in diagnostic criteria (visual field test or self-report) and heterogeneity in the racial and genetic background of participants [16]. More recently, L/Z, which are highly concentrated along the macular level of the retina, have been investigated in patients with POAG [16]. Given that the macular pigment optical density (MPOD) has been significantly associated with glaucoma-related structural parameters such as the optic disc rim area, ganglion cell complex (GCC) thickness, and thickness of the inner retina ($p = 0.02–0.05$), L/Z represent a promising avenue for future research and therapy [16].

What lessons learned from AREDS could help with designing a clinical trial for glaucoma? Currently, there is insufficient evidence to determine whether the AREDS formula benefits glaucoma patients. Studies have produced mixed findings due to variations in patient cohorts, confounding variables such as other consumed nutrients, insufficient dosage, and diagnostic criteria [23]. Thus, there is a need to develop a randomized controlled trial to investigate the relationship between antioxidants and the incidence and progression of glaucoma. Based on the evidence, the nutrients in the AREDS formula, especially L/Z, are excellent

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Received: 13 December 2021 Revised: 12 January 2022 Accepted: 19 January 2022
Published online: 29 January 2022

Table 1. The effects of age-related eye disease study (AREDS) nutrients on glaucoma.

Nutrient	Mechanism	Results: Pro	Results: Con
Vitamin C	• blood pressure and IOP lowering [6] • antioxidant effects that protect RGCs [7]	• low and high-dose consumption linked with decreased odds of glaucoma [8] • decreased levels seen in normal-tension glaucoma patients [9]	• unrelated to glaucoma prevalence in one study [10]
Vitamin E	• antioxidant effects that improve RGC survival and decrease changes in trabecular meshwork cells [11]	• Coenzyme Q10 with vitamin E drops improves inner retinal function and visual cortical responses [12] • rats with vitamin E deficient diet had more RGC death [13]	• no association between dietary antioxidant use and risk of POAG [10]
Beta-Carotene	unknown	• no significant isolated correlation seen between beta-carotene and reduced incidence of glaucoma or improved outcomes in glaucoma patients	• potentially increased risk of lung cancer in former or current smokers [3]
Copper	unknown	• no significant isolated correlation seen between copper and reduced incidence of glaucoma or improved outcomes in glaucoma patients	• no evidence that copper affected visual field, RNFL or GCC thickness in POAG cases [14]
Lutein and Zeaxanthin (L/Z)	• dietary antioxidants whose concentration is upregulated in the macular region [15] • protect retinal pigment epithelium from oxidative stress [16]	• serum concentrations of L/Z were positively associated with retinal blood flow, which is linked to glaucoma risk [17, 18] • more consumption of green leafy vegetables associated with reduced risk of incident POAG [19] • MPOD has been significantly associated with glaucoma-related structural parameters [20, 21]	• no significant correlation was found between use of vitamins and carotenoids and risk of POAG [10]
Zinc	unknown	• no significant isolated correlation seen between zinc and reduced incidence of glaucoma or improved outcomes in glaucoma patients	• no evidence that zinc affected visual field, RNFL or GCC thickness in POAG cases [14]

candidates. We recommend that (1) the trial includes patients who are at risk according to glaucoma severity or have low levels of the studied nutrients, (2) it is critical to develop endpoints in addition to IOP to monitor disease status. Retinal nerve fibre layer (RNFL) and macular imaging are likely more sensitive and reliable objective endpoints than visual field testing in glaucoma patients and should be considered in trial design, and (3) a well-designed trial requires adequate length, preferably at least 10 years, and sufficient sample size considering loss of follow-up or mortality. All in all, this much needed well-executed trial, like AREDS, may provide new insights; it may demonstrate the benefits of antioxidant therapy in conjunction with IOP lowering on preserving the RNFL, especially in the most vulnerable patients with the lowest baseline level of the studied nutrients.

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AUTHOR CONTRIBUTIONS

AS and TSV contributed to the literature reviews, preparation, and approval of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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