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(REVIEW ARTICLE)

Attenuation of the onset and progression of age-related vision impairments by reducing oxidative stress and inflammation by micronutrients

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Abstract

The major eye diseases refractive error, cataract, age-related macular degeneration (ARMD), glaucoma, and diabetic retinopathy can lead to blindness without an early intervention. The treatments include eye glasses for refractive error, surgery for cataract, and medications for glaucoma and ARMD. These therapies do not address oxidative stress and inflammation that contribute to these eye diseases. Therefore, supplementation with antioxidants could be useful. However, administration with single or multiple dietary antioxidants with or without carotenoids (zeaxanthin and lutein), and omega-3-fatty acids, produced no benefits or only modest benefits in certain eye diseases. The problems associated with such antioxidant's approaches were identified, and potential causes for not producing optimal benefits were presented. The major objectives are to show that enhanced oxidative stress and inflammation contribute to the age-related major eye diseases. This review presents rationales for using a comprehensive mixture of micronutrients containing dietary and endogenous antioxidants, vitamin D3, and carotenoids such as lutein, zeaxanthin, astaxanthin, all B-vitamins, and minerals Zn and Se for simultaneously reducing oxidative and inflammatory damage. Since elevated levels of vascular endothelial growth factor (VEGF) are found in the wet ARMD and diabetic retinopathy, this mixture has ingredients, which reduce VEGF levels. Supplementation with this micronutrient mixture may delay the onset and progression of major eye diseases, and may improve the effectiveness of standard therapy.

Keywords: Eye diseases; Antioxidants; Free radicals; Pro-inflammatory cytokines; Protection

1. Introduction

The major vision impairments include refractive error, cataract, age-related macular degeneration (ARMD), glaucoma, and diabetic retinopathy, which can lead to blindness without an early intervention. There are approximately 1.3 million Americans who are legally blind. Visual impairment is one of the major health concerns nationally and internationally. In addition to the advancing age, the genetic, environmental, lifestyle, and dietary factors can influence the time of onset, progression, and severity of the eye diseases. The number of individuals with vision diseases and blindness is increasing because of increased lifespan in the USA. It is estimated that the number will continue to increase in future. Therefore it is imperative that an effective prevention and improved treatment strategies are developed.

Refractory error is caused by changes in the lens structure, while cataract is due to the opacity of the lens. Age-related macular degeneration is caused by damage to the retina and is characterized by the presence of Drusen (yellowish deposit) of varying sizes beneath the retinal pigment. Glaucoma is caused by reduction in fluid draining system resulting into increased pressure in the eye, while diabetic retinopathy is caused by damage to the vascular system in the eye.

Table 1 shows the prevalence of major eye diseases in the USA, such as refractive error, cataract.

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Table 1 Prevalence of major eye diseases in the USA (in million)

Year	ARMD	Glaucoma	Cataract	Diabetic retinopathy	Refractive Error
2014	2.1	2.7	24	7.7	48.2
2030 *	3.7	4.3	38.7	11	59

ARMD (Age-related macular degeneration) In 2014, refractive error includes 34.1 million myopia (near-sighted) and 14.1 million hyperopia (far-sighted); In 2030, refractive error includes 39 million myopia and 20 million hyperopia. *Estimated value of prevalence; From the National Institute of Eye, NIH, Eye Disease Statistics, 2014

ARMD, glaucoma, and diabetic retinopathy. From these data, it appears that these vision impairments are of serious health concerns among adults 50 years and older. Table 2 shows the incidence of major eye diseases in ethnic groups in the USA. The incidence of ARMD was higher in non-Hispanic whites than Hispanics and African Americans, while glaucoma incidence in African Americans was higher than other ethnic groups. Hispanics have the highest incidence of cataract and diabetic retinopathy compared to other ethnic groups.

Table 2 Percent incidence of major eye diseases in ethnic groups in the USA

Ethnic Groups	ARMD	Glaucoma	Cataract	Diabetic retinopathy	Others
Non-Hispanic White	28.1	2.3	42.2	4.7	22.7
Hispanic	14.5	6.4	48.0	15. 0	16.2
African Americans	7.8	11.3	41.7	12	27.0

ARMD (Age-related macular degeneration); From American Academy of Ophthalmology: US Eye Disease Statistics, 2012

Despite the use of corrective glasses, refractory error continues to progress requiring new glasses every few years. This is due to the fact that corrective glasses do not affect oxidative stress and inflammation that contribute to the development of this disease. Similarly, cataract can be treated effectively with surgery, which does not have any impact on the above cellular defects involved in the pathogenesis of opacity. The glaucoma, ARMD, and diabetic retinopathy are not easily treatable.

Increased oxidative stress and inflammation are major contributors to the initiation and progression of vision impairments. In cases, where abnormal proliferation of blood vessels is involved, increased levels of vascular endothelial growth factor (VEGF) contribute to the progression of such eye diseases. Therefore supplementation with antioxidants and an inhibitor of VEGF should be useful in such eye diseases.

The transparent vitreous body, which occupies 80% of eye volume, is composed of 98-99% of water, very small amounts of collagen fibers, glycosaminoglycan, non-collagenous proteins, and trace minerals. It also contains enzymatic and non-enzymatical antioxidants that protect vitreous body from oxidative damage (1, 2). Thus, it is important that as we grow older, the vitreous body of the eye should continue to be filled with sufficient amounts of antioxidants in order to delay the onset and progression of the major eye diseases.

In the normal eye, the vitreous body helps to maintain low oxygen concentration surrounding the lens (3). In a highly myopic eye, lens is exposed to increased oxidative stress due to the presence of high concentration of oxygen, which contributes to the degeneration of the vitreous body leading to an early onset of cataract (4). Increased oxidative stress causes hypermethylation of antioxidant enzymes genes that deceases the expression levels of antioxidant enzymes, which cause an early development of cataract in the myopic eye (5).

This review shows that enhanced oxidative stress and inflammation contribute to the age-related major eye diseases. Previous antioxidant approaches produced limited benefits in reducing the progression of certain eye diseases. The lack of the full spectrum of micronutrients in the experimental designs may have contributed to minimal beneficial effects Therefore a comprehensive mixture of micronutrients containing dietary and endogenous antioxidants together with lutein, zeaxanthin, and astaxanthin, all B-vitamins, Se and Zn, which may simultaneously reduce oxidative and inflammatory damage is proposed. Such a micronutrient mixture would delay the onset and progression of eye diseases, and may improve the efficacy of standard therapy.

2. Oxidative Stress and Inflammation in Major Eye Diseases

Oxidative stress and inflammation is closely linked. If the oxidative damage of cells is not healed, chronic inflammatory responses occur. Such inflammatory responses release ROS, pro-inflammatory cytokines, complement proteins, and adhesion molecules that can cause cell death in the eyes.

2.1. Refractory error

Increased oxidative stress occurs in patients with myopia (6) and in all major eye diseases (7). High myopia is the leading cause of blindness. Levels of markers of oxidative stress, hepatocyte growth factor (HGF), and nitrite/nitrate ratio were elevated, while the levels of VEGF were reduced in the aqueous humor samples from patients with high myopia undergoing cataract surgery (8). Increased oxidative stress leads to increased inflammatory responses by producing enhanced amounts of NF-kB, a pro-inflammatory cytokine. The expression levels of c-Fos, NF-kB, IL-6, and TNF-alpha were also upregulated in the myopic eye, suggesting the role of chronic inflammation in the pathogenesis of myopia (9). High myopia causes thinning of retinal pigmented epithelial (RPE) cells leading to suppression of its function that results in depletion of VEGF in the aqueous humor (10).

2.2. Age-related macular degeneration (ARMD)

There are two forms of ARMD dry form and wet form. Dry form contributes to about 85-90% of all ARMD cases. In the wet form of ARMD abnormal blood vessels starts to grow beneath the retina (neovascularization) that allows fluid and blood to leak out giving the appearance of wet ARMD. It is the leading cause of loss of vision. Increase oxidative stress and inflammation cause degeneration of retinal epithelial cells leading to death of photoreceptors and ultimately loss of vision (11, 12). The macula is continuously exposed to high levels of oxidative stress. Tobacco smokers (13, 14) and high fat diet (15, 16), which generate excessive amounts of free radicals, further enhance oxidative damage to the macula accelerating the rate of progression of ARMD. Oxidative damage in the eye induces inflammatory responses which play an important role in the progression of ARMD. A recent review show that complement proteins and pro-inflammatory cytokines released from chronic inflammatory responses contribute to the pathogenesis of ARMD (17).

The wet ARMD is associated with increased levels of VEGF that cause neovascularization in the retina (18). Alpha-tocopheryl succinate), the most effective form of vitamin E (19), inhibits VEGF (20); therefore, this form of vitamin E, could be useful in the management of the eye diseases with an elevated level of VEGF.

2.3. Cataract

The incidence of cataract is high in countries with excessive sun light (21) which causes photochemical reaction in the eye producing excessive amounts of ROS that damages the lens (22). Increased oxidative stress is associated with the development of cataract (23-25)

2.4. Glaucoma

There are two forms of glaucoma open-angle glaucoma and close-angle glaucoma. Open-angle glaucoma is the most common form of glaucoma, which contributes to approximately 90% of all glaucoma cases. It develops gradually and the symptoms are difficult to detect. It had wide and open angle between iris and cornea. Normal-tension glaucoma is a form of open-angle glaucoma with normal eye pressure. About one-third of open-angle glaucoma represents this form of glaucoma. On the other hand, close-angle glaucoma has a close and narrow angle between iris and cornea (26). Excessive production of ROS plays an important role in the pathogenesis of primary open-angle glaucoma (POAG), which is a major contributor to the development of irreversible blindness worldwide (27, 28). The levels of malondialdehyde (MDA), a marker of oxidative stress, were elevated, while the levels of total antioxidant capacity declined in the blood and aqueous humor of patients with glaucoma (29). It was reported that production of ROS was caused by damage to the vascular system due to unstable blood flow resulting into an unstable oxygen supply (30). Furthermore, oxidative stress occurred primarily in the mitochondria of retinal ganglionic neurons and their axons causing the death of ganglion cells.

Glaucoma is characterized by degeneration of retinal ganglion cells and their axons in the optic nerve. Evidence for an early inflammatory responses initiated by activated astrocytes, microglia, and blood-derived immune cells are found at the optic nerve head (ONH), suggesting a role of inflammation in the pathogenesis of glaucoma (31-33)

Increased intraocular pressure occurs due to a reduction in the drainage of axoplasmic fluid (29). In patients with glaucoma, increased production of aqueous humor caused an elevation of intraocular pressure that led to the death of retinal ganglion neurons (34).

2.5. Diabetic retinopathy

Diabetic retinopathy is considered a microvascular complication of diabetes, which is the leading cause of blindness. Increased oxidative stress plays an important role in the onset and progression of diabetic retinopathy (35-39). Increased markers of inflammation are also found in patients with diabetic retinopathy (40-42). Activated retinal microglia migrate to the site of inflammation and produce pro-inflammatory cytokines, ROS, nitric oxide, glutamate , and proteases, which contribute to the degeneration and eventually the death of retinal ganglion cells (43-45). In addition to increased oxidative stress and chronic inflammation, enhanced the levels of VEGF, which contributes to both vascular permeability and angiogenesis, occurs in rodent models (46)

3. Role of Carotenoids alone in the Management of Major Eye Diseases

Several studies have been performed in determining the benefits of one or more carotenoids in certain eye diseases. These studies are described here.

3.1. Astaxanthin in animal studies

Astaxanthin, a carotenoid, accumulates selectively in the eye. It protects retinal cells in vitro and in mice against oxidative stress (47). It also reduced oxidative and inflammatory damage in the retinal cells of diabetic rats (48). Astaxanthin decreases oxidative stress and inflammation, improves immune response (49, 50), reduces apoptosis in retinal ganglion cells, and retinal pigmented epithelial cells in rodents (51, 52).

3.2. Lutein and zeaxanthin in epidemiologic studies

The analysis from the Growing Up in Singapore towards Healthy Outcomes (GUSTO) cohort showed that high levels of maternal plasma concentration of carotenoids lutein and zeaxanthin were associated with improved visual acuity of the offspring (53). Extensive epidemiologic studies have revealed conflicting results on the beneficial effects of antioxidants in the management of major eye diseases. This review has focused on only intervention investigation with one or more micronutrients.

4. Individual Antioxidants or Minerals in Eye Diseases

The use of individual antioxidants or minerals produced inconsistent results in patients with ARMD (54).

5. Role of a Mixture of Dietary Antioxidants with or without Carotenoids in Eye Diseases

These studies and their limitation are describe below under each eye disease

5.1. Refractory error

5.1.1. A mixture of dietary antioxidants together with carotenoids in refractory errors in dogs

Like human, dogs also show age-related decline in vision. Treatment with dietary antioxidants (vitamin C, vitamin E. and beta-carotene) together with eye carotenoids (lutein, zeaxanthin, and astaxanthin) for a period of six months slowed down the development of refractory error and improved retinal and visual function in the dogs (55). This formula lacks endogenous antioxidants, vitamin D3 as well as B-vitamins and minerals selenium and Zn. Therefore such micronutrient mixture may not produce desired benefits in human eye disease.

5.2. Age-related macular degeneration (ARMD)

5.2.1. A mixture of dietary antioxidants and zinc in ARMD

In the initial AREDS (Age-Related Eye Disease Study), oral supplementation with a mixture of vitamin C, vitamin E, beta-carotene, and zinc modestly decreased the risk of progression of ARMD and vision loss (56). This micronutrient mixture lacks endogenous antioxidants, vitamin D3, carotenoids lutein, zeaxanthin and astaxanthin, all B-vitamins, and selenium and zinc; therefore, may not produce optimal benefits.

In the AREDS2, a mixture of dietary antioxidants (high-dose vitamin C and vitamin E) together with lutein and zeaxanthin and minerals zinc and copper modestly reduced the progression of ARMD. Addition of DHA (docosahexaenoic acid) plus EPA (eicosapentaenoic acid) to this formula showed no further benefit (57). Inclusion of beta-carotene increased the risk lung cancers among smokers. Another study reported that lutein and zeaxanthin

without beta-carotene would be appropriate in reducing the risk of progression of ARMD (58). This micronutrient mixture lacks other dietary and endogenous antioxidants, vitamin D3, astaxanthin, B-vitamins, Se and Zn. The addition of astaxanthin is essential because it exhibits the most powerful antioxidant and anti-inflammation activities compared to other carotenoids (59). Unlike most antioxidants, which protect inner layer or outer layer of the cellular membrane against oxidative damage, astaxanthin protects both layers against such damage (60, 61). In addition, high-dose of zinc (80 mg) in this micronutrient mixture may induce copper deficiency by reducing the absorption of copper from the intestine (62, 63). Copper in this formula may also interact with vitamin C to generate excessive amounts of free radicals (64). Therefore, this micronutrient mixture may not produce desired benefits in improving the management of eye diseases.

5.2.2. A mixture of B-vitamins in Eye Diseases

Daily supplementation with a mixture of certain B-vitamins, such as folic acid, vitamin-B6, and vitamin-B12 reduced the risk of ARMD in women (65). This mixture lacks all dietary and endogenous antioxidants, vitaminD3, carotenoids, and minerals Se and Zn.

6. Cataract

6.1. One or a mixture of antioxidants in Catarct

Supplementation with vitamin C protected light-induced damage to the ocular lens (66). The Antioxidant in Prevention of Cataract (APC) Study with a follow-up period of 5 years revealed that a mixture of vitamin C, vitamin E and beta-carotene did not affect the progression of cataract in the population of South India (67). Supplementation of beta-carotene alone was ineffective in reducing the progression of cataract (68). Antioxidants/mineral supplement decreased the risk (69), and attenuated the progression of cataract (70). Supplementation with a mixture of vitamin E, vitamin C, and beta-carotene for a period of 3 years produced a small rate of reduction in the progression of cataract (71).

7. Glaucoma

7.1. A mixture of antioxidants, omega-3-fatty acids, and minerals in Glaucoma

Glaucoma and dry eye disorder (DED) frequently appear as a comorbid. Open-angle glaucoma had elevated levels of TNF-alpha, IL-6, and VEGF compared to non-severe DED glaucoma, and it had higher levels of Il-6 than control subjects. Oral administration of a mixture of antioxidants (vitamin A, vitamin C, vitamin E, and glutathione), Omega 3 fatty acids DHA (decosahexaenoic acid) , EPA (eicosahexaenoic acid), DPA (decosapentaenoic acid), minerals (zinc, copper, manganese, and selenium), and tyrosine and cystenine reduced IL-6 and TNF-alpha in patients with open-angle glaucoma (72). This micronutrient mixture lacks endogenous antioxidants, carotenoids, and B-vitamins. Copper interacts with vitamin C to generate excessive amounts of free radicals. Studies on animal models of glaucoma suggest that lutein protects retina from oxidative damage (73).

8. Diabetic Retinopathy

8.1. A single antioxidant or a mixture of dietary antioxidants in diabetic retinopathy

Because of involvement of oxidative stress and inflammation in diabatic retinopathy, animal and human studies suggest that antioxidants may be helpful in prevention and improved management of this eye disease (74). A mitochondrial antioxidant enzyme Mn-SOD (manganese-dependent superoxide dismutase) is impaired in diabetic retinopathy. Therefore activation of this antioxidant enzyme may prevent mitochondrial dysfunction by scavenging superoxide. Supplementation with alpha-lipoic acid, a co-factor of Mn-SOD, prevented apoptosis of retinal capillary cells and the development of diabetic retinopathy in rats (37). A mixture of vitamin C, vitamin E, and beta-carotene did not reduce the risk of diabetic retinopathy in humans (75). Vitamin B1 (thiamine) treatment protected retinal pericytes against apoptosis in experimental model (76)

9. Rationale for Administering a Comprehensive Mixture of Micronutrients in the Eye Diseases

9.1. Failure of single antioxidants

Some potential reasons for the failure of a single antioxidant to yield expected benefits that were observed in animal models, but not in humans, are described here.

- Eye is exposed to high levels of ROS all the time. Administration of a single antioxidant in a high oxidative environment of the eye would be oxidized, which then would act as a pro-oxidant rather than as an antioxidant.
- Different antioxidants are distributed differently and in different amounts in the sub-cellular compartments of the cells of the eye, all of which must be protected. Administration of a single antioxidant cannot accumulate in all parts of the cell in sufficient amounts to provide an adequate protection against oxidative damage.
- Vitamin E is more effective scavenger of free radicals in reduced oxygen pressure, whereas beta-carotene and vitamin A are more effective in higher oxygen pressure of the cells (77). Since eye pressure varies in some eye diseases such as glaucoma, administration of one antioxidant may not provide adequate protection throughout the eye.
- Elevation of both antioxidant enzymes, dietary and endogenous antioxidant compounds as well as carotenoids lutein, zeaxanthin, astaxanthin are needed to achieve maximal protection against oxidative damage in the entire eye. This is due to the fact that they act by different mechanisms. Antioxidant compounds neutralize free radicals by donating electrons to those atoms in the molecules with unpaired electrons, whereas antioxidant enzymes destroy H202 by catalysis, converting them to harmless molecules such as water and oxygen. Administration of a single antioxidant alone cannot achieve this goal.
- Administration of a single antioxidant cannot protect both the aqueous and lipid compartments of the cells in the eye against oxidative damage.
- Different antioxidants increase the production of different protective proteins in the cells by altering the expression of different microRNAs (78). For example, some antioxidants can activate Nrf2 by upregulating miR-200a that inhibits its target protein Keap1, whereas others activate Nrf2 by downregulating miR-21 that binds with 3'-UTR Nrf2 mRNA (79). Thus, different antioxidants activate Nrf2 (Nuclear Factor-Erythroid-2- Related Factor 2) by different mechanisms. Administration of a single antioxidant cannot accomplish the above objective.

9.2. Problems associated with previous micronutrient approaches

As discussed earlier, various mixture of micronutrients used in previous eye disease studies produced only modest reduction in progression of some eye diseases. This could be attributed to the lack of the full spectrum of micronutrients in mixture, which can simultaneously decrease oxidative and inflammatory damage in the eye.

10. How to simultaneously Reduce Oxidative Stress and Inflammation in the Eyes

In order to reduce oxidative stress and inflammation at the same time, it is essential to simultaneously enhance the levels of antioxidant enzymes and dietary and endogenous antioxidant compounds (80). Oral supplementation with a mixture of antioxidants can increase the levels of dietary and endogenous antioxidant compounds; however, enhancing the levels of antioxidant enzymes require an activation of a nuclear transcriptional factor Nrf2. A brief description of the activation of Nrf2 processes is presented here.

10.1. Activation Processes of Nrf2

Under normal physiological conditions, reactive oxygen species (ROS) is required to activate Nrf2. Activated Nrf2 dissociates itself from Keap1- CuI-Rbx1 complex in the cytoplasm and migrates to the nucleus where it heterodimerizes with a small Maf protein and binds with ARE (antioxidant response element) leading to increased transcription of cytoprotective enzymes including antioxidant enzymes (81-85).

During the prolonged oxidative stress commonly observed in human chronic diseases, activation of Nrf2 becomes resistant to ROS (86-88). This is evidenced by the fact that increased oxidative stress continues to occur in chronic diseases despite the presence of Nrf2. However, some antioxidants such as alpha-tocopherol and genistein (89, 90), alpha-lipoic acid (91), curcumin (92), resveratrol (93, 94), omega-3-fatty acids, (95, 96), glutathione (97), n-acetylcysteine (98), and coenzyme Q10 (99) can activate this ROS-resistant Nrf2.

Activation of Nrf2 alone is not adequate to enhance the levels of antioxidant enzymes. Activated Nrf2 must then bind to ARE in order to promote the transcription of genes coding for antioxidant enzymes.

10.2. Activated Nrf2 and antioxidant compounds attenuate inflammation

It has been reported that activation of Nrf2 decreases oxidative stress as well inflammation (100, 101). Many antioxidant compounds also attenuate inflammation (102-107).

11. Proposed Mixture of Micronutrients may Reduce the Onset and Progression of Major Eye Diseases.

A comprehensive mixture of micronutrients containing vitamin A, mixed carotenoids, vitamin C, alpha-tocopheryl acetate, alpha-tocopheryl succinate, vitamin D3, alpha-lipoic acid, N-acetylcysteine, coenzyme Q10, curcumin, resveratrol, lutein, zeaxanthin, astaxanthin, all B-vitamins, and minerals selenium, and zinc for delaying the onset and progression of major eye diseases is proposed. This mixture would increase the levels of antioxidant enzymes by activating the ROS-resistant Nrf2 and enhancing the levels of dietary and endogenous antioxidant compounds. Such a micronutrient mixture may optimally and simultaneously reduce oxidative stress and chronic inflammation, and thereby, provide a maximal protection against oxidative and inflammatory damage in the eye. This micronutrient mixture may delay the onset and progression of major eye diseases.

12. Conclusion

The major eye diseases, such as refractive error, cataract, age-related macular degeneration (ARMD), glaucoma, and diabetic retinopathy are serious health concerns for people 50 years and older. They can lead to blindness without early intervention. The current practices for improving the eye-sight do not address the issue of increased levels of oxidative stress and inflammation that contribute to the onset and progression of these eye diseases. Therefore, supplementation with antioxidants could be useful in reducing the risk of these diseases. Studies suggest that supplementation with dietary antioxidants with or without lutein, zeaxanthin, omega-3-fatty acids has reduced somewhat the progression of certain eye diseases. However, these mixture of micronutrients lacked several ingredients that are necessary for simultaneously reducing oxidative stress and inflammation in the eye. The rationale for using a comprehensive mixture of micronutrients containing dietary and endogenous antioxidants, vitamin D3, lutein, zeaxanthin, astaxanthin, all B-vitamins, and minerals Zn and Se for simultaneously reducing oxidative and inflammatory damages is proposed. This mixture also contains d-alpha-tocopheryl succinate that can reduce the levels of vascular endothelial growth factor (VEGF) in eye diseases, such as wet (ARMD) and diabetic retinopathy, which have elevated levels of VEGF. Supplementation with this proposed micronutrient mixture may delay the onset and progression of major eye diseases, and may improve the efficacy of standard therapy. Pre-clinical and clinical studies to test the efficacy of this micronutrient mixture for reducing the risk of development and progression of each major eye disease are recommended.

Compliance with ethical standards

Disclosure of conflict of interest

The author is Chief Scientific Officer of Engage Global, inc. of Utah. This company sells nutritional products to consumers.

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