Eye Health, Eye Diseases, and Eye Protection by Nutraceuticals

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Evidence-Based Use of Supplements

ABSTRACT

Visual impairment is a major public health and a humanitarian crisis – it is associated with a reduced quality of life because it makes it more difficult to carry out everyday activities such as driving, reading, and meal preparation. Visual impairment leads to an increased risk of poorer overall health, social isolation, falls, and depression. The annual cost of visual impairment and blindness in people over 40 years old in the U.S. is estimated to be $5.5 billion.1,2 The Eye Diseases Prevalence Research Group estimated that about 3.4 million U.S. adults above 40 suffer from visual impairment, and this figure in 2020 would reach 5.5 million.1

Diabetic retinopathy, glaucoma, cataracts, and age-related macular degeneration (AMD) are major causes of blindness around the world. The Eye Diseases Prevalence Research Group has estimated that by 2020 over 30 million Americans will develop cataracts. The same group predicted that 2.2 million Americans over 40 will be diagnosed with glaucoma by 2020 and that 4.1 million Americans will be diagnosed with diabetic retinopathy during that same year.1 Diabetic retinopathy, glaucoma, cataracts, and AMD are all age-related degenerative diseases, and they all share some common etiological pathways. These pathways broadly include inflammation, apoptotic factors, and oxidative stress, which provide potential therapeutic targets for treatment and prevention.2,3

We have reached a point, thanks to extensive clinical trials, where a variety of nutraceuticals have demonstrated their effectiveness at postponing or preventing these devastating eye diseases. With eye disease incidence growing at an accelerating rate along with the aging population, developing effective treatments is called for simply from a humanitarian point of view. This review is dedicated to helping us understand what these eye diseases are, the causes and contributing factors involved, and what clinical trials have revealed about potential therapeutics that could be used to postpone or prevent these diseases.

Factors Contributing to Age-Related Eye Diseases and the Structure of the Eye

Eye tissues have a high metabolic rate and are at or are closely approaching a condition of oxidative stress, where there is an excessive generation of reactive oxygen species (ROS) beyond the body's ability to protect itself against their damaging effects. The eye tissues and the aqueous humor of the eye have high levels of hydrogen peroxide because of this high metabolism.4,5 The retina, with its abundance of rod and cone cells, are especially vulnerable to mitochondrial damage. The mitochondria are the energy-producing organelles in cells and account for 91% of oxygen reductions that generate an enormous volume of free radicals.

Photoreceptor cells are specialized types of cells in the retina that convert light into electrical signals. The two major photoreceptor cells are the rods and the cones. The retina is composed of six million cone cells and 120 million rod cells. Photoreceptor proteins in the cells absorb photons and convert them into electrical impulses. The photoreceptor cell's mitochondria perform at their maximum respiratory capacity, with a very limited reserve of 20%, and are quite literally living in a state of continuous oxidative stress.6 This means that their free radical production easily exceeds their ability to quench the free radicals generated in many cases. Retinyl cells are working at maximum energy output and this may explain, in part, their vulnerability to diseases of the eye.

Another factor that is unique in explaining diabetic retinopathy, glaucoma, cataracts, and age-related macular degeneration (AMD) is that the retina, rods, and cones are exposed to ultraviolet light damage that generates singlet xygen, a ROS that further damages mitochondria in these tissues.7,8 The highly concentrated levels of lutein, zeaxanthin and meso-zeaxanthin found in the macula, the oval area at the center of the retina, provide the macula with its pigmented color.

This paper will explain each eye disease and which nutrients have been successful in the prevention or slowing of the progression of each of these diseases.

Diabetic Retinopathy and Clinical Trials Using Nutritional Supplements

Diabetic retinopathy is a condition that occurs in diabetics, where, over time, hyperglycemia damages the blood vessels in the retina causing the retinyl blood vessels to leak blood and other fluids. This phenomenon causes the retinal tissue to swell, causing blurred or cloudy vision. Diabetic retinopathy usually affects both eyes. The longer patients have diabetes with untreated hyperglycemia, the more likely they are to develop diabetic retinopathy.

A contrast sensitivity test measures your ability to distinguish between finer and finer increments of light versus dark. Contrast sensitivity is a very important measure of visual function and low contrast sensitivity can be a symptom of diabetic retinopathy. Contrast sensitivity is also an accurate measure of the appearance or the progression of diabetic retinopathy.

In a study of type-1 and type-2 diabetics treated with 300 milligrams (mg) of alpha lipoic acid for 3 months, the group of patients with type-1 diabetes had their contrast sensitivity remain stable and the contrast sensitivity improved in the type-2 diabetics. Contrast sensitivity became worse after 3 onths in the untreated group. According to the study's authors, "our results suggest that supplementation with ALA represents an achievable adjunct therapy to help prevent loss of vision in diabetic patients."9

A study of 1,353 patients with type 2 diabetes diagnosed between 1993 and 1995 was conducted where nutrient intake was assessed with a food-frequency and supplement questionnaire. Pre-existing diabatic retinopathy was determined from graded photographs. The study concluded that there was no association of diabetic retinopathy with Vitamin C or E intake either from food or from supplements.10

Non-proliferative diabetic retinopathy is an early stage of diabetic retinopathy. One study compared serum lutein and zeaxanthin concentrations between patients with non-proliferative diabetic retinopathy and normal subjects, and the effects of supplementation with Lutein and zeaxanthin on visual function in non-proliferative diabetic retinopathy. Serum lutein and zeaxanthin concentrations were significantly lower in non-proliferative diabetic retinopathy patients than in normal control subjects. Lutein at 6 mg per day and zeaxanthin at 0.5mg per day caused the serum lutein/zeaxanthin levels in the non-proliferative diabetic retinopathy group to be higher than those in normal controls after one month. The average contrast sensitivity after 3 months of lutein/zeaxanthin supplementation increased significantly. Visual acuity also improved significantly after medication in the diabetic retinopathy group.11

A randomized clinical trial, Prevencion con Dieta Mediterranea(PREDIMED), demonstrated that consuming 500 mg or more per day of long-chain omega-3 polyunsaturated fatty acids led to a decreased risk of diabetic retinopathy in middle-aged and older type 2 diabetics. During a six-year follow-up, a 48% reduction of diabetic retinopathy was noted.12 A systematic review of studies on dietary intake and the incidence of diabetic retinopathy concluded that "Dietary fiber, oily fish, a Mediterranean diet and a reduced caloric intake are associated with lower risk of DR."13

Human trials with alpha lipoic acid, lutein, zeaxanthin, and omega-3-fatty acids have provided guidelines for the effective dose of each nutrient to treat diabetic retinopathy. The supplement industry is rife with formulas that only have 'window dressing' amounts of nutrients. These manufacturers often cite clinical trials using effective doses, but then formulate their products with sub-standard amounts, sometimes far below the amounts cited in the studies. It is up to the consumer to read the ingredients label to see if each individual ingredient is comparable to the amounts used in clinical trials. Manufacturers sometimes use 'proprietary blends' to disguise the fact that suboptimal amounts of nutrients are present in their formulas.

In the case of alpha lipoic acid, successful clinical trials use 300 mg per day that are needed to achieve good results at restoring contrast sensitivity in diabetic retinopathy patients. Any formula providing less than 6 mg per day of lutein and 0.5 mg of zeaxanthin are suboptimal amounts and should be avoided. Regarding omega-3-fatty acids, 500 mg or more decreases the risk of diabetic retinopathy in large clinical trials, any amount less than 500 mg daily is a suboptimal amount.

Cataract Prevention and Treatment with Nutritional Supplements

The Age-Related Eye Disease Study 2 (AREDS2), a large intervention trial whose first endpoint was to evaluate the effect of supplementation of lutein and zeaxanthin on reducing risk of progression to advanced AMD, secondarily measured the effect of these compounds on cataract development or cataract surgery. Supplementation with 10 mg of lutein and 2 mg of zeaxanthin for 5 years resulted in a 30% reduction of developing any cataract and a 32% reduction of cataract surgery compared to no supplementation.14

Cataractous lenses often have dramatic decreases in glutathione (GSH) levels, up to 81%, compared to normal lenses.15 The question of whether low GSH is due to decreased synthesis or increased degradation has finally been answered. Decreases in the enzymes required for the synthesis and recycling of GSH from oxidized glutathione (GSSG) is the reason that glutathione levels are much lower in cataractous lenses. Researchers have found that normal human and rabbit lenses with high glutathione levels were rapidly capable of detoxifying hydrogen peroxide in cell studies.16

Evidence suggests that alpha lipoic acid can help prevent diabetic cataract formation.17 Lipoic acid exists as either R-lipoic acid or S-lipoic acid. R-lipoic acid by itself effectively prevented cataract formation. The higher efficacy of R-lipoic acid as compared to alpha-lipoic acid is related to the higher rate of R-lipoic acid absorption by the lens.18

Carotenes, xanthophylls, and vitamin A all have antioxidant properties, are all singlet oxygen quenchers, and are all found in the cells, the lens, and the aqueous humor of the eye. Carotenes and xanthophylls help redox recycle glutathione from its oxidized form back to its reduced antioxidant form. A prospective study of the effect of carotenes and vitamin A on the risk of cataract formation was carried out as part of the Nurses' Health Study. 77,466 female nurses, ages 45-71 years, were included in the study, which used food-frequency questionnaires over a 12-year period. After other risk factors were controlled for, subjects in the highest quintile of lutein and zeaxanthin intake had a 22% decreased risk of cataract formation compared to those in the lowest quintile.19

Another continuation of the Nurses' Health Study observed 50,823 women for eight years. The results showed that women in the highest quintile of vitamin A intake had a 39% lower incidence of cataracts than women in the lowest quintile.20 A study of 36,644 U.S. male health professionals 45-75 years, were followed for eight years with dietary questionnaires of carotenoid intake and other dietary factors. Other subjects were included as they reached the age of 45. During 8 years of follow-up, 840 subjects had senile cataract extraction. Men in the highest quintile of lutein and zeaxanthin dietary intake had a 19% decreased risk of cataract development or treatment.21 Ingestion of other carotenoids, beta carotene, lycopene, alpha carotene, or beta-cryptoxanthin had no effect on cataract risk in either the women's or in the men's studies.22

A Swedish study of Total Antioxidant Capacity (TAC) and the risk of developing cataracts was conducted in 2014. The advantage of measuring TAC in human blood serum has the advantage over other interview methods in that it directly measures the impact of dietary sources of antioxidants, bypassing inter-individual bioavailability issues. Over 30,000 women 49 years and older were followed for 7.7 years. Not surprisingly, the women with the highest Total Antioxidant Capacity had the lowest risk of developing cataracts. The study authors noted that the primary sources of antioxidants were fruit and vegetables, whole grains and coffee, accounting for 44.3%, 17.0% and 15.1% respectively of the TAC.23

This study is in accord with a 2008 study of female health professionals where the risk of cataract development was lower with an increased dietary intake of lutein, zeaxanthin, and vitamin E. Women with highest intake of lutein and zeaxanthin had an 18% lower risk of developing cataracts. Higher dietary or supplemental vitamin E was associated

with a 14% lower risk of developing cataracts in the study.24

A prospective analysis in the Nutrition Vision Project (NVP), showed that women aged 60 years or older who consumed at least 363 mg per day of vitamin C had a 57% decreased risk of developing cataracts compared with women who consumed less than 140 mg per day of vitamin C. Women who took vitamin C as a supplement for 10 years or longer had less cortical lens opacities than women not supplementing.25

AMD and Clinical Trials with Nutritional Supplements
The purpose of the first AREDS study was to explore the association of mortality and vitamin-mineral effects in normal patients and those with varying degrees of macular degeneration. In terms of ocular health and the progression of AMD, the study showed no associations between vitamins C, E, and beta carotene in slowing the progression AMD. It is fair to raise the question of why lutein and zeaxanthin were not included in the study, and the answer is that these essential nutrients in 1992 were not at the forefront of ocular research nor even mentioned in the study references cited.26 (26) However, AREDS1 did show a weak association that Zinc taken alone reduced the risk of developing AMD. These weak associations with Zinc and AMD prevention contradict other studies that show no association with dietary

Zinc intake and AMD development or progression. A study of 66,572 women and 37,636 men followed for 10 years showed no association between Zinc intake and the risk of developing AMD.27 Antioxidants plus Zinc in AREDS1 further lowered the risk of AMD by 4% and vision loss by 1%, statistically insignificant amounts. In the AREDS study, fish oil also failed to have any significant long-term benefits. The AREDS study, despite using large populations followed over many years, failed to find that vitamin E, C, Beta carotene, Zinc or fish oil had any effect on the development or progression of AMD.

Lutein and zeaxanthin are widely recommended as dietary supplements for the prevention of visual loss because they specifically quench singlet oxygen and prevent lipid peroxide damage.28,29 Lutein and zeaxanthin must be obtained from dietary sources such as green, orange, and yellow fruits and vegetables, while meso-zeaxanthin is believed to be mainly converted from Zeaxanthin in the body. Supplementation with lutein, zeaxanthin and meso-zeaxanthin increases the macular pigment optical density (MPOD) in human trials where these three nutrients were given to healthy people or patients with AMD. In human trials where meso-zeaxanthin was included along with lutein and zeaxanthin in the supplements given to the study subjects, the MPOD was greater than simply by giving lutein and zeaxanthin alone.30

The first study to measure whether meso-zeaxanthin was absorbed in a supplement and whether it improved MPOD was conducted with ten subjects given 20 mg of mostly meso-zeaxanthin with some lutein and zeaxanthin present. present. The study lasted 120 days and used a placebo group.

The study authors concluded that “a supplement containing the macular carotenoids, lutein, zeaxanthin and meso-zeaxanthin, but principally meso-zeaxanthin, is effective at raising MPOD in most subjects. Increased MPOD may be an effective means of protecting the aging population from AMD.” Interestingly, the authors further concluded that “the efficiency of conversion of lutein to meso-zeaxanthin is generally below 50%. Thus, there may be an advantage in providing meso-zeaxanthin in a supplement at the expense of lutein if the goal is to raise the overall zeaxanthin level and potentially improve the degree of retinal protection.30

Any good eye support formula should have optimal amounts of meso-zeaxanthin in addition to lutein and zeaxanthin listed on the ingredients panel.

A 2010 study of 22 healthy persons given a supplement with predominantly meso-zeaxanthin for six months confirmed that optimal MPOD was achieved using this formulation. The researchers concluded that “Our findings are consistent with previous supplementation studies that have shown increases in serum concentrations of lutein and zeaxanthin and MPOD following supplementation with the macular carotenoids. Interestingly, the greatest increase seen in this study was at the center following supplementation with an meso-zeaxanthin dominant formulation.” 31

A 2001 study of human donor eyes had previously demonstrated that donors in the highest quartile of macular pigment had an 82% lower risk of having AMD compared to donors in the lowest quartile.32 The retinas from 56 donors with AMD and 56 normal retinas were uses as controls.

Lutein, zeaxanthin and meso-zeaxanthin supplementation increases MPOD which lowers the risk of developing AMD and slows the progression of AMD. This effect has been demonstrated in up-to-date clinical trials and in reviews of clinical trials.33–36
In a study of dietary flavonoids and the prevalence and incidence of AMD, 2,856 adults 49 years or older were followed up for 15 years. An increase in the dietary intake of total flavonols and total flavanones was associated with reduced odds of the incidence of developing any AMD. A significant trend was noted between an increased intake of total flavanones and Hesperidin (a citrus bioflavonoid) and a lower risk of developing AMD 15 years later. Study volunteers who reported consuming more than one serving of oranges per day compared with those who never ate oranges had a lower risk of AMD incidence 15 years later.37

Consumers should consider buying an eye health formula with Hesperidin listed on the ingredients panel.

Glaucoma and Clinical Trials with Nutritional Supplements
Glaucoma is a common eye condition where the fluid pressure inside the eye rises to a higher level than is normal for the human eye. Left untreated, glaucoma may damage the optic nerve, causing loss of vision or complete blindness. The pathogenesis of glaucoma is not fully understood, but intraocular pressure is the most critical and treatable risk factor. Intraocular pressure is regulated by the balance between aqueous humor secretion and its outflow from the eye. Open-angle glaucoma is a type of glaucoma defined by an open, normal appearing anterior chamber angle in the eye and raised intraocular pressure with no other underlying disease.

In the Rotterdam Study, 3,502 participants aged 55 years and colder supplied dietary data for an average follow-up of 9.7 years to establish a relationship between vitamin and mineral intake and the incidence of developing open-angle glaucoma. The study authors concluded that the participants who developed incident open-angle glaucoma had a lower intake of beta carotene, retinol, vitamin B1 and vitamin B12 compared to those who did not develop open angle glaucoma. No other differences in nutrition were found between those who did or did not develop the disease.38

A study of supplementation with either Bilberry extract or Gingko biloba extract in patients with normal tension glaucoma was conducted with a follow-up between 12 to 59 months in some cases. Normal tension glaucoma is an open-angle glaucoma where damage to the optic nerve and visual

field occur although intraocular pressure is within the normal range. The study involved 332 patients, 78 of whom had diabetes mellitus, and 103 had hypertension. The study authors concluded that "Our results suggest that systemic administration of anthocyanins (Bilberry) and Ginko Biloba extract improves visual function in some individuals with NTG" . . . "We think that the mechanisms of anthocyanins and GBE action are effects on blood circulation and antioxidant properties." 39 A study of 79 subjects with intraocular pressure were treated with pine bark and bilberry extracts in one group and another group was treated with the drug latanoprost as eye drops. A third group was treated with bilberry, pine bark and latanoprost. Those who received the pine bark-bilberry combination began to show a statistically significant drop in intraocular pressure beginning at the sixth week of treatment that reached a maximum 24% reduction at 16 weeks. The group given the pine bark-bilberry supplements alone did not reach the exact same level of pressure lowering with latanoprost alone, but when the bilberry-pine bark extract was combined with the drug, the intraocular pressure dropped 40%.40

A study of persons with high intraocular pressure but no signs of glaucoma were given a bilberry-pine bark extract mixture for up to 18 months. After two months of supplementation the average intraocular pressure decreased from 25.2 mmHg to 22.2 mmHg. (millimeters of mercury). No further improvement was found after six months.41

Consumers should look for an eye health formula that contains Bilberry extract on the label, and better yet if Gingko biloba or Pine bark extract are listed on the ingredients panel because they provide additive or synergistic effects when Bilberry is present in the formula as seen in the above clinical trials.

Persons with glaucoma often develop dry eye syndrome. Dry eye syndrome in glaucoma cans simply be a concurrent condition with glaucoma or can result from treatment with antihypertensive eye drop medications. An oral nutraceutical formulation based on omega-3 polyunsaturated fatty acids, vitamins, minerals, and antioxidants was found to be effective at treating dry eye syndrome in patients with glaucoma.42 Supplementing with Korean red ginseng is also effective in relieving dry eye syndrome in 49 glaucoma patients treated for eight weeks with Ginseng.43

A study of 105 adults with normal intraocular pressure were divided into three groups. Group one was given an oral omega-3 supplement, krill oil, with 945 mg/day of EPA + 510 mg/day of DHA ± 900 mg/day α-linolenic acid or a placebo, an olive oil 1,500 mg per day supplement. The third group was given fish plus flaxseed oils (900 mg/day EPA + 600 mg/day DHA + 900 mg/day AŁA. After 90 days, intraocular pressure was reduced to 13.6 mm of mercury in the omega-3 group krill oil group, and the placebo group had a slight intraocular pressure increase to 14.2 mm of mercury. The study authors concluded that "Our data demonstrated that 3 months of systemic omega-3 supplementation significantly reduces IOP in young normotensive adults consuming a typical Western diet. To our knowledge, this is the first prospective clinical study to report that omega-3 fatty acids directly modulate IOP in humans. Our findings indicated a modest (8%) reduction in IOP." Interestingly, an 8% drop in intraocular pressure is the average pressure drop seen with drugs used to treat elevated intraocular pressure.44

Studies on diabetic retinopathy with omega-3-fatty acids and studies with omega-3's from marine sources that support lowering intraocular pressure provide the consumer with guidelines when buying an eye health formula. You should check the ingredients panel to see if it provides 900 mg of EPA and at least 500 mg of DHA because this is what the successful ocular studies use.

The Side Effects of Prescription Drugs for Treating Eye Disorders

The eyes are extremely sensitive to drugs and it is not surprising that vision can be impaired by using prescription drugs. AMD is usually treated by direct injections into the eyeball with a group of drugs known as anti-vascular endothelial growth factors (anti-VEGF). Aside from the painfulness of the procedure itself, anti-VEGF drugs have common serious side effects, that include raising intraocular pressure and seeing spots that follow the eye's movements caused by air bubbles that enter through the injection side. Rarer side effects include inflammation inside the eye, retinyl damage and the development of cataracts.45,46

Prescription drugs to treat cataracts include a class of drugs known as alpha-1 adrenergic antagonists. When used at any time before cataract surgery, the surgery is made more difficult and it increases the chances of complications from the surgery. The serious side effects of its use before eye surgery are often irreversible. This includes reducing pupil dilation, causing a loss of dilator tone and tissue atrophy of the iris, resulting in Intraoperative Floppy Iris Syndrome, or IFIS.47,48

Drugs to treat glaucoma include rho kinase inhibitors, beta blockers and alpha agonists, usually made as eye drops but are sometimes formulated as tablets. Ocular surface irritation can occur with any type of eye drop used. Rho kinase inhibitor side effects commonly include redness of the eye, bleeding spots on the whites of the eye, stinging, and corneal deposits. Beta blocker side effects include hypotension (low blood pressure), shortness of breath, lower than normal pulse rate and fatigue. Hypotension and low pulse rates are obviously the most dangerous side effects of beta blockers. The common side effects of alpha agonists include a greater chance of having an allergic reaction, dry mouth and nose, drowsiness, headache and burning of the eyes.49

Summary

Human clinical trials have identified several promising nutraceuticals for treating specific eye diseases – diabetic retinopathy, cataracts, AMD, and glaucoma. In clinical trials of patients with diabetic retinopathy, alpha lipoic acid, lutein and zeaxanthin have been shown to improve contrast sensitivity. Supplementation of long-chain omega-3 fatty acids over six years resulted in a 48% reduction of developing diabetic retinopathy.

Lutein, zeaxanthin and meso-zeaxanthin supplementation in clinical trials has been shown to increase MPOD, which lowers the risk of developing AMD and slows the progression of AMD. Dietary intake of total flavonols and total flavanones was shown to reduce the risk of developing AMD. The citrus bioflavonoid Hesperidin lowered the risk of developing AMD over a 15-year follow-up.

Persons in the highest quintile of vitamin A intake had a 39% lower incidence of cataracts than those in the lowest quintile. Those people in the highest quintile of lutein and zeaxanthin dietary intake had a 19% decreased risk of cataract development or treatment. The risk of cataract development was lower with an increased dietary intake of lutein, dietary or supplemental vitamin E was associated with a 14% lower risk of developing cataracts. Persons aged 60 years or older who consumed at least 363 mg per day of vitamin C had a

57% decreased risk of developing cataracts compared to those who consumed less than 140 mg per day of vitamin C. People who supplemented for 10 years or longer had less cortical lens opacities.

In glaucoma studies, higher intake of beta carotene, retinol, vitamin B1, and vitamin B12 lowered the risk of developing the disease. Omega-3 supplementation significantly lowered intraocular pressure 8% using krill oil high in EPA and DHA. Dry Eye Syndrome, which is often experienced by people suffering from glaucoma, has been successfully treated with a mixture of omega-3 fatty acids, antioxidants, vitamins, and minerals. Korean red ginseng supplementation has also been used successfully to treat dry eye syndrome in glaucoma patients.

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