Dynamic Chiropractic

NUTRITION / DETOXIFICATION

Antioxidants in the Prevention and Management of Eye Diseases

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In recent years a number of animal studies, epidemiological studies and small intervention trials of human subjects have suggested that certain antioxidants may significantly reduce the risk of cataracts and age-related macular degeneration. These studies also indicate that high-dose antioxidant supplementation may halt or retard the further progression of these conditions if introduced during early- stage disease.

For years there has been much debate on this subject among top-ranking researchers and ophthalmologists. In spite of the encouraging results reported in some studies, the official position statement of these authorities indicated inconclusive evidence to support the clinical use of antioxidant supplementation in high-risk patients and for the population at large, in regards to the prevention and management of cataracts and age-related macular degeneration. However, the positive outcomes reported in several small trials prompted the National Eye Institute (NEI) to sponsor a large multicenter trial aimed at determining whether antioxidant supplementation is a useful intervention in age-related macular degeneration. The much-anticipated results of this study, known as the Age-Related Eye Disease Study (AREDS), were published in October 2001 in the *Archives of Ophthalmology.*

The AREDS study was an intervention trial involving 4,757 patients between 55 and 80 years old. The results of this landmark study revealed that patients who were at high risk of developing more advanced stages of age-related macular degeneration (AMD) were shown to have reduced their risk by approximately 25 percent when treated with a high-dose combination of vitamin C, vitamin E, beta-carotene, and zinc. According to the NEI, this is the first effective treatment that has been shown to successfully slow the progression of AMD. Participants in this double-blind, placebo-controlled clinical study, who suffered from varying degrees of AMD, were given one of four treatments: zinc alone; antioxidants alone; a combination of antioxidants and zinc; or a placebo. After 6.3 years of treatment, the results showed that taking zinc alone (80 mg per day, plus 2 mg of copper) or antioxidants alone (500 mg of vitamin C, 400 IU of vitamin E, and 25,000 IU of beta-carotene per day) were effective interventions, but the best results occurred in those taking both antioxidant and zinc supplements at the above described doses. These intake levels greatly exceed levels of these vitamins and minerals that are customarily attained from food alone, or can be derived from food alone in most cases. Thus, supplementation has emerged as the only viable course of action to achieve these results.

This study represents a major breakthrough in how supplementation is viewed. This is one of few circumstances where a study that met all the gold standards of research methodology has provided unquestioned evidence that the use of a specific vitamin supplement protocol has been established as the only proven treatment for this important medical condition.

Recommendations from the Age-Related Eye Disease Study

Although all the details of the underlying causes of AMD are not fully understood, it has been shown that free radical damage from ultraviolet light (sunlight) reaching the macula is likely a significant contributing factor. It has also been shown in previous studies that certain antioxidants can protect the macula from UV-light-induced free radical damage, and thus may be an important intervention in the treatment and management of AMD. Based upon the findings of the age-related eye disease study, the researchers conclude that all persons older than 55 years should have dilated eye examinations to determine their risk of developing advanced AMD. Those with extensive intermediate size drusen (fatty or fibrous deposits under the retina), at least one large drusen, noncentral geographic atrophy in one or both eyes, or advanced age-related macular degeneration or vision loss due to AMD in one eye, and without contraindications to the use of antioxidant or zinc supplementation, should consider taking a supplement of antioxidants plus zinc at the same or similar doses used in this study. Age-related macular degeneration is the leading cause of blindness in people over the age of 55 in the U.S., Canada and in most developed countries around the world.[1] As such, any safe and effective low-cost intervention that can prevent the development of AMD or significantly slow its progression would save the health care system enormous sums of money and improve the quality of life for many thousands of members of our aging society.

It is estimated that 150,000 Americans are legally blind from AMD, with 20,000 new cases occurring per year. In addition to the effects of ultraviolet light, other risk factors for AMD include smoking, advancing age, atherosclerosis and high blood pressure.[2]

Previous Studies Demonstrating Antioxidant Protection in AMD

Earlier studies have provided evidence that more optimal status of antioxidant vitamins and minerals could reduce the risk of AMD. In one study, higher blood levels of antioxidants were shown to be related to a lower risk of developing AMD.[3] Another investigation revealed that individuals in the top 20 percent of blood levels of selenium, vitamin C and vitamin E had a 70-percent lower risk of developing AMD than those with blood levels in the lowest 20 percentile.[4] In the physicians' health study, male doctors taking vitamin E supplements had a 13-percent reduced risk of AMD. Risk was reduced by 10 percent in those taking a multiple vitamin and mineral, after controlling for other confounding variables.[5]

Two previous intervention trials, using a commercially available broad-based antioxidant formula in patients with established AMD, demonstrated that supplementation halted or significantly slowed the further progression of the disease; in some cases, vision improved. These studies were only six months and 18 months, and the research and medical community demanded a longer term, multi center, double-blind, placebo-controlled study to confirm these findings. This was the impetus for the design and implementation of the age-related eye disease study reviewed above. In these previous intervention trials the supplement formula contained beta-carotene; vitamin C; vitamin E; zinc; copper; manganese; selenium; and riboflavin.[6]

Zinc plays a vital role in the eye. It is required by two important enzymes in the retina that are in part responsible for vision.[7] Zinc also is required as the prosthetic group for an important antioxidant enzyme known as superoxide dimutase. In the absence of the prosthetic group, superoxide is unable to function as an antioxidant. Selenium participates in a similar way with respect to the antioxidant

enzyme known as glutathione peroxidase.[8] A double-blind trial supplementation of 45 mg of zinc significantly reduced the rate of visual loss in people with AMD over a one-to-two-year period.[7] However, a second study failed to show a protective effect when zinc supplementation was tested in 112 patients with AMD.[9]

Other studies indicate that certain carotenoids are also important antioxidants in the prevention and management of AMD. The macula, especially the central portion (the fovea) owes its yellow color to high concentrations of lutein and zeazanthin. These yellow carotenes function as macular pigments that absorb photon energy from ultra-violet light, which may otherwise cause free radical damage to the retina. Dietary intake of lutein and zeazanthin (mostly dark green vegetables) and supplementation with these two carotenoids has been shown to significantly increase the amount of macular pigment.[10,11,12,13] One study showed that adults with the highest intake of lutein had a 57-percent reduced risk of developing AMD than did those with low levels of this carotenoid.[14] In an intervention trial with 16 participants (13 with retinitis pigmentosa and three with other retinal degeneration problems), vision improved significantly after 26 weeks of supplementation with lutein (40 mg for six weeks, followed by 20 mg for 20 weeks). These researchers have shown similar results in small trials involving patients with AMD, as well.[15] Harvard researchers reported that adults consuming an average 5.8 mg per day of lutein-zeazanthin had a 57-percent decreased risk of developing AMD, compared with subjects ingesting less than this amount.[16] Other investigations have demonstrated a strong correlation between higher intake levels of lutein-zeazanthin and a lower risk of AMD.[17]

The evidence linking free radical damage to the development of AMD is strong and consistent. Sunlight triggers oxidative damage to the eye, which in turn leads to macular degeneration.8 Animals given antioxidants have been shown to lower risk of visual problems in experimental studies.[19]

Flavonoids and AMD

There are also some specific flavonoid compounds that are known to concentrate in the macula in a similar fashion as certain carotenoids. These flavonoid compounds not only enhance the macular pigment and exert antioxidant effects, but improve blood flow and help stabilize fragile blood vessels, as often occurs in cases of diabetic retinopathy. Clinical studies in humans have demonstrated that all three of the following flavonoid-based supplements are capable of aiding in the treatment of AMD.[20,21,22,23] The standardized grade of bilberry (25 percent anthocyanidin content) concentrates as part of the visual purple of the retina, helping to reduce free radical damage. Bilberry flavonoids (anthocyanidins) also reduce capillary fragility by improving collagen integrity and reduced capillary permeability. This is most important in cases where diabetic retinopathy is present and in the prevention of diabetic retinopathy, as indicated by its use in certain parts of Europe. The therapeutic dose of bilberry in these cases requires 40-80 mg, up to three times per day.[25]

A double-blind study indicated that ginkgo biloba extract improved long-distance visual acuity in cases of macular degeneration and diabetic retinopathy. The therapeutic dose for this purpose is 40-80 mg two to three times per day, using a standardized grade of 24 percent ginkgo-flavone glycosides and six percent terpene content.[26]

Grape seed extract may also be useful in the prevention and management of AMD and diabetic retinopathy. The flavonoids in grape seed extract are known to strengthen the wall of blood vessels and provide antioxidant protection. Like lutein-zeazanthin, bilberry flavonoids and certain other antioxidants, flavonoids from grape seed extract have been shown to concentrate in the area of the macula (as well as in other tissues). Preliminary studies have implicated its role as an intervention, which can help preserve retinal function in diabetics and myopic patients. The therapeutic dose for this application is 150-300 mg per day, using a standardized grade of 95 percent proanthocyanidolic compounds.[27,28] Thus, it may be prudent to include some or all of these interventions in patients at high risk for these retinal conditions, in addition to the doses and nutrients used in the age-related eye disease study.

Cataracts and Antioxidants

Cataracts are white, opaque lesions that form on the transparent lens of the eye. They occur as a result of damage to the protein structure of the lens. In recent years it has been identified that oxidative stress (free radicals) is a major contributing factor to the development of age-related (senile) cataracts, and normal antioxidant protective mechanisms in the lens have been found to be significantly compromised in cases where senile cataracts occur. Strong evidence indicates that oxidative stress from ultra violet light (sunlight) and radiation exposure induces free radical damage to the lens that contributes to senile cataracts development. The lens of the eye is devoid of antioxidant enzymes, superoxide dismutase (SOD), catalase and glutathione peroxidase, and is completely dependent upon nutritional antioxidants, including vitamin E, vitamin C, selenium and carotenes for its antioxidant defenses. Cigarette smoking, which also increases oxidative stress to the body, is a known risk factor for the development of cataracts.[29,30]

Cataracts are the leading cause of blindness and impaired vision in the U.S. Forty thousand Americans are blind due to cataracts, and cataract surgery is the most prevalent major surgery among Medicare recipients in the U.S.[29] In Canada, there were an estimated 884,000 prevalent cases of senile cataracts in 1988, and a further 330,000 new cases, plus 1.2 million cases of senile lens changes expected by the end of 1993. In Canada, each cataract surgery cost $3,000 on average in 1991. The Canadian study by J. Robertson, et al., suggested that if everyone over 55 took appropriate doses of vitamin C and vitamin E each day, it would reduce cataract incidence by at least 50 percent and cut related health care costs in half.[31] A number of intervention trials have demonstrated that 1,000 mg of vitamin C per day (or more) can reduce cataract development or halt or slow the further progression of cataracts in the early stages.[32,33,34] Other case-control and prospective studies have suggested that higher blood levels and/or intake levels of vitamin C are associated with a significant reduction in risk of cataracts. For instance, in a study by P. Jacques, plasma vitamin C at 40 umol/L was associated with an 11.3 times greater risk of cataract development than occurred in subjects with a plasma level of 90 umol/L or higher.[29,35]

Vitamin E supplementation has also been shown to protect against cataracts. A dosage of 400 IU was shown to be effective in this regard, whereas a dosage of only 50 IU failed to provide protection against cataract development in a double-blind trial.[36,37,38,39]

The intake of lutein-zeazanthin-rich vegetables, such as spinach, kale and broccoli, is also linked to a reduction in cataract risk, which may be as sizeable as a 20-22 percent reduction. This data stems

from large prospective studies, including the Beaver Dam eye study (n=1,354), the nurses' health study (n=50,461) and the health professionals follow-up study (n=36,644).[40,41,42,43] Curiously, the antioxidant carotenoids, lutein and zeazanthin are known to be present in the lens of the eye, whereas beta-carotene is not.[42] Animal studies have demonstrated that melatonin, which possesses antioxidant properties, blocks the formation of cataracts under experimental conditions and a Chinese formula, known as *hachimijiogan (baweiwan),* has been used successfully in the treatment of cataracts. This formulation contains a variety of antioxidant-rich herbs.[29,44]

Finally, diabetics are at increased risk for cataract development, primarily due to the buildup of sorbitol in the lens of the eye that occurs under uncontrolled hyperglycemic conditions. The lens lacks the ability to break down sorbitol, which leads to morphological changes associated with cataract development. The flavonoid quercetin, when supplemented (500 mg, one to three times per day), is an effective aldose reductase inhibitor, which blocks the conversion of glucose to sorbitol and thus, may be considered as an additional supplementation intervention in diabetic patients to help further reduce the risk of cataracts.[45]

Summary and Conclusion

The results of the age-related eye disease study confirm that antioxidant supplementation is an effective means by which an individual can prevent and/or slow the underlying metabolic activities that lead to advanced and clinically important age-related macular degeneration. The body of evidence also suggests that antioxidant supplementation may prevent early stage development of both cataracts and age-related macular degeneration, and thus has the potential to markedly reduce financial costs to the health care system and improve the quality of life for millions of individuals. Consuming more fruits and dark green leafy vegetables, not smoking, and implementing lifestyle behaviors to prevent or better manage diabetes should be emphasized as preventive measures. However, the use of antioxidant supplements at levels beyond which an individual can customarily consume from food alone, has emerged as an extremely important practice through which these eye conditions may be prevented and/or treated. All primary health care practitioners should be aware of the importance of these findings and be able to direct patients to appropriate nutrition, lifestyle and supplementation interventions and community resources that can help prevent and better manage these prevalent eye diseases.

References

1. Jampol LM, et al. Age-related eye disease study research group (collective name-AREDS). A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta-carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no.8. *Arch Ophthalmol* 2001 Oct;119(10):1417-36.
2. Murray M, Pizzorno J. *Encyclopedia of Natural Medicine* (2nd edit) Prima Health 1998;319-324.
3. West S, et al. Are antioxidants or supplements protective of age-related macular degeneration? *Arch Ophthalmol* 1994;112:222-227.
4. Eye disease case-control study group. Antioxidant status and neovascular age-related macular degeneration. *Arch Ophthalmol* 1993;111:104-109.
5. Patient risk factors; antioxidants and maculopathy. *Nurses' Drug Alert* 23,1999;6:45.
6. Olson RJ. Supplemental antioxidant vitamins and minerals in patients with macular

degeneration. *J Am Coll Nutr* 1991;10:550/Abstract 52.
7. Newsome DA, et al. oral zinc in macular degeneration. *Arch Ophthalmol* 1988;106:192-198.
8. Halliwell B, Gutteridge J. *Free Radicals in Biology and Medicine* (2nd edit.), Oxford University Press 1991;218-266.
9. Stur M., et al. Oral zinc and the second eye in age-related macular degeneration. Invest Ophthalmol 1996,37:1225-1235.
10. Hammond BR, Jr., et al. Density of the human crystalline lens is related to the macular pigment carotenoids, lutein and zeazanthin. *Optom Vis Sci* 1997;74;7:499-504.
11. Landrum JT, et al. The macular pigment: A possible role in protection from age-related macular degeneration. *Adv Pharmacol* 1997;38:537-556.
12. Landrum JT, et al. Macular pigment stereomers in individual eyes. *Invest Ophthalmol Vis Sci* 1995; 38:1795-1801.
13. Hammond BR, et al. Dietary modification of human macular pigment density. *Invest Ophthalmol Vis Sci,* 1997;38:1795-1801.
14. Seddon JM, et al. Dietary carotenoids, vitamin A, C, and E and advanced age-related macular degeneration. *JAMA* 1994;272:1413-1420.
15. Dagnelie G, et al. Lutein improves visual function in some patients with retinal degeneration: a pilot study via the Internet. *Optometry* 2000;71;3:147-164.
16. Seddon JM, et al. Dietary carotenoids, vitamin A, C, and E and advanced age-related macular degeneration. *JAMA* 1994;272:1413-1420.
17. Mares-Perlmen JA, et al. Serum antioxidants and age-related macular degeneration in a population-based case control study. *Arch Ophthalmol* 1988;113:1518-1523
18. Young RW. Solar radiation and age-related macular degeneration. Surv *Ophthalmol* 1988;32:252-59
19. Katz ML, Parker KR, Handelman GJ, et al. Effects of antioxidant nutrient deficiency on the retina and retinal pigment epithelium of albino rats: a light and electron microscopic study. *Exp Eye Res* 1982;34:339-59.
20. Scharrer A, et al. Anthocyanosides in the treatment of retinopathies. *Klin Monatsbl Augenheilked.* 1981;178:386-389.
21. Caselli L, et al. Clinical electro-retinographic study on the activity of anthocyanosides. *Arch Med Int* 1985;37:29-35.
22. Lebuisson DA, et al. Treatment of senile macular degeneration with ginkgo biloba extract: A preliminary double-blind versus placebo study. *Presse Med* 1986;15:1556-1558.
23. Corbe C, et al. Light vision and Chorioretinal circulation: Study of the effect of procyanidolic oligomers. *J Fr Ophthalmol* 1988;11:453-460.
24. Wegmann R, et al. Effects of anthocyanosides on photoreceptors: Cytoenzymatic aspects. *Ann Histochim* 1969,14:237-256.
25. Murray M. *The Healing Power of Herbs* (2nd edit). Prima Publishing, 1995:50-59.
26. DeFeudis FV. (ed.). Ginkgo biloba extract (Egb-761): *Pharmacological Activities and Clinical Applications.* Elsevier, Paris 1991.
27. Soyeux A, et al. Endotelon: Diabetic retinopathy and hemorrheaology (preliminary study) *Bull Soc Ophthalmol Fr* 1987;87:1441-444.
28. Proto F, et al. Electrophysical study of Vitis Vinifera procyanoside oligomers effects on retinal function in myopic subjects. *Ann OH Clin Ocul* 1988;11:453-460.
29. Murray M, Pizzorno J. *Encyclopedia of Natural Medicine,* 2nd edition. (Prima Publishing) 1998;319-24.
30. Varma S. Scientific basis for medical therapy of cataracts by antioxidants. *Am J Clin Nutr* 1991;53;1:335-345 (suppl).
31. Robertson J, et al. A possible role for Vitamin C and E in cataract prevention. *Am J Clin Nutr.* 1991;53;1:346-351 (suppl).

32. Bouton S, et al. Vitamin C and the aging eye. *Arch Int Med* 1939;63:930-945.
33. Atkinson D. Malnutrition as an etiological factor in senile cataract. *EENT Monthly,* 1952;31:79-83.
34. Ringwold A, et al. Senile cataract and ascorbic acid loading. *Acta Opthalmol* 1985;63:277-280.
35. Jacques PF, et al. Epidemiologic evidence of a role for the antioxidant vitamins and carotenoids in cataract prevention. *Am J Clin Nutr* 1991;53;1:352-355 (suppl).
36. Robertson J, et al. A possible role for vitamin C and E in cataract prevention. *Am J Clin Nutr* 1991;53;1:346-351 (suppl).
37. Lyle BJ, et al. Antioxidant intake and risk of incident age-related nuclear cataracts in the Beaver Dam study. *Am J Epidemiol* 1999;149:801-809.
38. Rouhiainen P. et al. Association between low plasma vitamin E concentration and progression of early cortical lens opacities. *Am J Epidemiol* 1996;144:496-500.
39. Teikari JM, et al. Long-term supplementation with alpha-tocopherol and beta-carotene and age-related cataract. *Acta Ophthalmol Scan* 1997;75:634-640.
40. Lyle BJ, et al. Antioxidant intake and risk of incident age-related nuclear cataracts in the Beaver Dam study. *Am J Epidemiol* 1999;149:801-809.
41. Jacques PF, et al. Epidemiologic evidence of a role for the antioxidant vitamins and carotenoids in cataracts prevention. *Am J Clin Nutr* 1991;53;1:352-355 (suppl).
42. Chasen-Taber L, et al. A prospective study of carotenoid and vitamin A intakes and risk of cataract extraction in U.S. women. *Am J Clin Nutr* 1999;70;4:509-516.
43. Brown L, et al. A prospective study of carotenoid intake and risk of cataract extraction in U.S. men. *Am J Clin Nutr* 1999;70;4:517-524.
44. Reiter RJ, et al. Oxygen radical detoxification process during aging: The functional importance of melatonin. *Aging Clinical Exp Res* 1995;7:340-351.
45. Chaundry PS, et al. Inhibition of human lens aldose reductase by flavonoids, sulindac and indomethacin. *Biochem Pharmacol* 1983;32;1995-1998.

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