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Nutrients and Eye Disease

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Introduction

Age-related cataract and age-related macular degeneration (AMD) are two of the leading causes of visual impairment in older Americans. Cataracts cloud the lens and impair the entry of light into the eye. AMD results in the loss of central vision due to impingement on the macula, which is responsible for absorption of short wavelengths of light. (See Figure 62.1 for anatomy of the eye.) Studies in animal models indicate a possible role for oxidative mechanisms in the development of both cataract and AMD. Available epidemiological data are derived primarily from observational studies and generally suggest small to moderate benefits for antioxidant nutrients in reducing the risks of cataract and AMD.

Antioxidant Nutrients and Cataract Prevention

There is increasingly strong evidence that the antioxidant nutrients vitamin C, vitamin E, and beta-carotene may help protect against cataracts. Vitamin C is 60 times more concentrated in the lens of the eye than in blood plasma, and other antioxidants, including lutein and other carotenoids, are also found in disproportionately high levels in the eye.

Taylor was among one of the first to suggest that adequate provision of antioxidants from multivitamins might help delay the development of cataracts.[1] This hypothesis was quickly verified by Sperduto et al. in the Linxian cataract studies[2] which showed that vitamin/mineral supplements, particularly niacin and riboflavin, may decrease the risk of nuclear cataract in an undernourished Chinese population. These were the first double-blind, randomized, well-controlled, long-term nutritional intervention studies using multivitamin/mineral supplementation to determine their effect on the prevalence of nuclear, cortical, and posterior subcapsular cataracts. Findings from the Sperduto studies suggested that vitamin/mineral supplements, especially the riboflavin and niacin components, may decrease the risk of nuclear cataract.

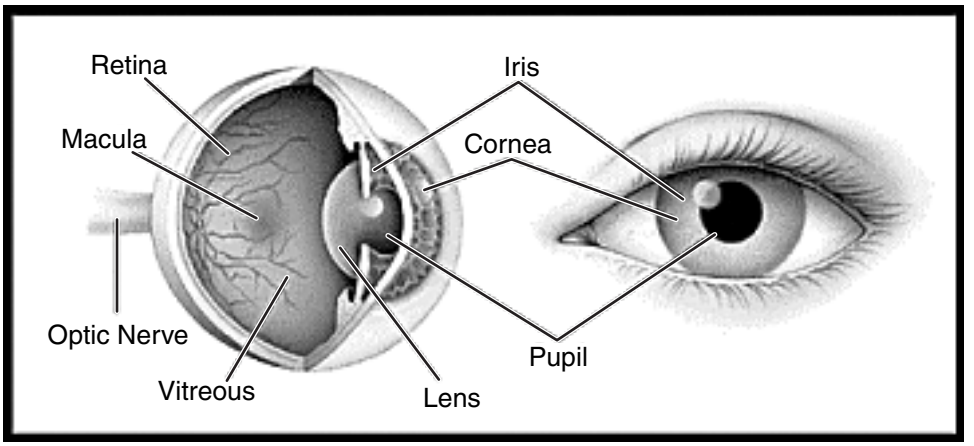

FIGURE 62.1
Anatomy of the eye.

TABLE 62.1

Vitamin E Intake or Plasma Concentration with Reduced Cataract Risk

Reference and Type of Study	Population (Duration)	Endpoint	Risk and Associated Intake or Plasma Concentration of Vitamin E
Jacques (1988)[7]	112 subjects	Plasma levels of vitamins E, C, and carotenoids	High plasma levels of at least two of the three antioxidants were associated with a reduced risk of cataract
Knekt (1992)[8]	47 patients with cataract and 94 controls	Plasma vitamin E and beta-carotene levels	Odds ratio for senile cataract risk was 2.6 for patients in lowest third of serum vitamin E and beta-carotene levels
Rouhaiinen (1996)[5]	410 males	Plasma vitamin E levels	Plasma vitamin E levels in the lowest quartile were associated with a 3.7-fold increased risk of progression of early lens opacities
Robertson (1989)[9]	175 individuals with cataract and 175 individuals without cataract	Vitamin E supplementation	There was a 56% decrease in cataract risk in subjects who took vitamin E supplements
Leske (1998)[6]	764 participants	Vitamin E supplement use and plasma levels	Risk of nuclear cataract was decreased by approximately 50% with regular vitamin E use and in subjects with higher plasma vitamin E levels
Lyle (1999)[10]	400 subjects	Serum carotenoids and tocopherol levels	Nuclear cataract may be linked inversely to vitamin E status but not with carotenoid status

Results of at least two large prospective cohort studies are consistent with a possible benefit of antioxidants in cataract. In the Physicians' Health Study, researchers found that users of multivitamins had a 27% lower risk of developing a cataract and a 21% lower risk of having a cataract operation, compared to non-users.[3] In the Nurses' Health Study, women in the highest quintile for total carotene intake had a 27% reduced risk of cataract.[4]

TABLE 62.2

Vitamin C Intake or Plasma Concentration with Reduced Cataract Risk

Reference and Type of Study	Population (Duration)	Endpoint	Risk and Associated Intake or Plasma Concentration of Vitamin C
Dietary Intake			
Robertson (1989)[9] Case-control	175 Cases, 175 controls	Cataract	>300 mg/d supplement: ↓ risk by 70%
Jacques and Chylack (1991)[11] Case-control	77 Cases, 35 controls	Cataract	>490 compared with <125 mg/d: ↓ risk by 75%
Hankinson (1992)[4] Prospective cohort	50828 Women (8 y)	Cataract (493 extractions)	705 compared with 70 mg/d: no ↓ risk; supplements for >10 y: ↓ risk by 45%
Vitale (1993)[12] Longitudinal	660 Men and women (6 y)	Cataract	>261 compared with <115 mg/d: no ↓ risk
Sperduto (1993)[2] Trial	3249 Chinese men and women (5 y)	Cataract	120 mg/d supplement: ↓ risk by 22% (NS) (+ 30 µg Mo/d cosupplement)
Jacques (1997)[13] Cross-sectional	247 Women (10 y)	Cataract	>359 compared with <93 mg/d: no ↓ risk; supplements for >10 y: ↓ risk by 77–83%
Plasma Concentration			
Jacques and Chylack (1991)[11] Case-control	77 Cases, 35 controls	Cataract	>90 compared with <40 µmol/L: ↓ risk by 71% (>400 compared with 80 mg/d)
Vitale (1993)[12] Longitudinal	660 Men and women (6 y)	Cataract	>80 compared with <60 µmol/L: no ↓ risk (>400 compared with 150 mg/d)

Adapted from Carr, AC, Frei, B. *Am J Clin Nutr* 69: 1086; 1999.

Data from two smaller cohort studies also support the association between antioxidant use and a reduced incidence of cataract. In a study of Finnish men with elevated cholesterol levels, those in the highest quartile of vitamin E intake had a three- to fourfold decreased risk of progression of early cortical lens opacities.[5] In the Longitudinal Study of Cataract, risk of nuclear cataract was reduced by one-third in regular users of multivitamins and by one-half in regular users of vitamin E supplements.[6]

Evidence is also accumulating to assist in characterizing the effect of individual antioxidant nutrients and their contribution to reducing the incidence of cataracts or slowing their progression. A number of epidemiologic studies have suggested an association between cataract incidence and blood levels of vitamin E or intake of vitamin E. These are listed in Table 62.1.

Several epidemiologic studies have investigated the association of vitamin C intake or plasma levels of vitamin C with the incidence of cataract. These are summarized in Table 62.2.

Exciting information concerning lutein and cataract risk has recently been reported from one observational study in men[14] and one in women.[15] Intakes of lutein and zeaxanthin were found to be inversely related to the risk of cataracts severe enough to require extraction. The role of lutein in the prevention of cataracts is discussed in an excellent review by Mares-Perlman.[16]

More research is needed on the impact that nutrient supplementation has on the risk of developing cataracts. Ongoing trials are listed at the end of this section along with

TABLE 62.3

Antioxidant Levels and Intakes and Risk of AMD

Reference	Study Size	Findings
West (1994)[19]	976	Plasma vitamin E levels in lowest quartile associated with two-fold risk of AMD
Smith (1999)[20]	3654	No association between antioxidant intake and risk of AMD
Tsang (1992)[21]	166	No association between vitamin E intake and risk of AMD
Mares-Perlman (1995)[22]	334	Plasma lycopene levels in lowest quintile associated with twofold risk of AMD
Seddon (1994)[23]	876	Carotenoid intake in the highest quintile was associated with a 43% decreased risk of AMD
Eye Disease Case-Control Study Group (1993)[18]	1036	High serum carotenoid levels are associated with a 2/3 risk reduction in AMD

trials examining the role of nutrients in age-related macular degeneration, which is discussed below.

Carotenoids and Acute Macular Degeneration

The macula is the part of the retina responsible for central vision and visual acuity. In primates, including humans, the central area of the macula is yellow due to presence of the "macular pigment," a high concentration of the carotenoids lutein and zeaxanthin. AMD occurs in about 20% of the population, is irreversible, and is the leading cause of visual impairment in the United States.

Supplementation with lutein has been found to increase serum levels of this nutrient, and also to increase macular pigmentation.[17] The Eye Disease Case-Control Study analyzed blood levels of antioxidant nutrients in 421 patients with AMD and in 615 controls. People with medium or high blood carotenoid levels had one-half and one-third the risk of AMD, respectively, compared to people with low carotenoid levels. Carotenoids analyzed were lutein, zeaxanthin, beta-carotene, alpha-carotene, cryptoxanthin, and lycopene. There was no significant protective effect of vitamin C, vitamin E, or selenium.[18]

Table 62.3 summarizes epidemiological studies of antioxidant intakes and plasma levels in association with the risk of AMD.

Recent data from cohort epidemiological studies show zinc to be weakly protective against the development of some forms of early AMD,[24] although this effect is not proven.[20] Newsome et al.[25] undertook the first prospective intervention study using daily doses of zinc 100 mg to determine its effect on visual acuity in subjects with drusen or AMD. Although some eyes in the zinc-treated group lost vision, this group had significantly less visual loss than the placebo group after a followup of 12 to 24 months.

Ongoing Trials

While the majority of evidence suggests a beneficial effect of antioxidants against the development and progression of cataracts and AMD, controlled intervention trials are

TABLE 62.4

Ongoing Trials Investigating Antioxidant Vitamins and Their Effect on Age-Related Cataract and AMD[26]

Trial	Study Population	Agents Tested
Age-Related Eye Disease Study	4753 men and women ages 55-80 with no AMD to relatively severe AMD	High-dose antioxidants (beta-carotene, vitamin C, vitamin E and zinc)
Physicians Health Study II	Approximately 15,000 healthy U.S. male physicians ages 55 and older	Beta-carotene 50 mg on alternate days Vitamin C 500 mg daily Vitamin E 400 IU on alternate days Multivitamin daily
Women's Health Study	39,876 healthy U.S. female health professionals ages 45 and older	Vitamin E 600 IU on alternate days
Collaborative Italian-American Clinical Trial of Nutritional Supplements and Age-Related Cataracts (CTNS)	1020 men and women with no or early cataract at entry	Daily multivitamin/multimineral supplement

Adapted from Christen, WG. *Proc Assoc Am Phys* 111: 16; 1999.

needed to more precisely define the protective role of antioxidants in preserving vision. Table 62.4 lists some ongoing trials.

References

1. Taylor A. *Ann NY Acad Sci* 669: 111; 1992.
2. Sperduto RD, Hu TS, Milton RC, et al. *Arch Ophthalmol* 111: 1246; 1993.
3. Seddon JM, Christen WG, Manson JE, et al. *Am J Public Health* 84: 788; 1994.
4. Hankinson SE, Stampfer MJ, Seddon JM, et al. *BMJ* 305: 335; 1992.
5. Rouhaiinen P, Rouhaiinen H, Salonen JT. *Am J Epidemiol* 144: 496; 1996.
6. Leske MC, Chylack LT, He Q, et al. *Ophthalmology* 105: 831; 1998.
7. Jacques PF, Chylack LT Jr, McGandy RB, et al. *Arch Ophthalmol* 106: 337; 1998.
8. Knekt P, Heliovaara M, Rissanen A, et al. *BMJ* 305: 1392; 1992.
9. Robertson J McD, Donner AP, Trevithick JR. *Ann NY Acad Sci* 570: 372; 1989.
10. Lyle BJ, Mares-Perlman JA, Klein BEK. *Am J Clin Nutr* 69: 272; 1999.
11. Jacques PF, Chylack LT. *Am J Clin Nutr* 53: 352S; 1991.
12. Vitale S, West S, Hallfrisch J, et al. *Epidemiology* 4: 195; 1993.
13. Jacques PF, Taylor A, Hankinson SE, et al. *Am J Clin Nutr* 66: 911; 1997.
14. Brown L, Rimm EB, Seddon JM, et al. *Am J Clin Nutr* 70: 517; 1999.
15. Chasan-Taber L, Willett WC, Seddon JM, et al. *Am J Clin Nutr* 70: 509; 1999.
16. Mares-Perlman JA. *Am J Clin Nutr* 70: 431; 1999.
17. Landrum JT, Bone RA, Kilburn MD. *Adv Pharmacol* 38: 537; 1997.
18. Eye Disease Case-Control Study Group. *Arch Ophthalmol* 111: 104; 1993.
19. West S, Vitale S, Hallfrisch J, et al. *Arch Ophthalmol* 112: 222; 1994.
20. Smith W, Mitchell P, Webb K, et al. *Ophthalmology* 106: 761; 1999.
21. Tsang NCK, Penfold PL, Snitch PF, et al. *Doc Ophthalmol* 81: 387; 1992.
22. Mares-Perlman JA, Brady WE, Klein R, et al. *Arch Ophthalmol* 113: 1518; 1995.
23. Seddon JM, Ajani UA, Sperduto RD, et al. *JAMA* 272: 1413; 1994.
24. Mares-Perlman JA, Klein R, Klein BE, et al. *Arch Ophthalmol* 114: 991; 1996.
25. Newsome DA, Swartz M, Leone NC, et al. *Arch Ophthalmol* 106: 192; 1988.
26. Christen WG. *Proc Assoc Am Phys* 111: 16; 1999.