Department of Veterans Affairs
Health Services Research & Development Service | Evidence-based Synthesis Program

HSR&D

Nutritional Supplements for Age-related Macular Degeneration: A Systematic Review

EXECUTIVE SUMMARY

January 2012

Prepared for:
Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service
Washington, DC 20420

Prepared by:
Evidence-based Synthesis Program (ESP) Center
Portland VA Medical Center
Portland, OR
Devan Kansagara, MD, MCR, Director

Investigators:
Principal Investigator:
Devan Kansagara, MD, MCR

Co-Investigators:
Ken Gleitsmann, MD, MPH
Melanie Gillingham, PhD, RD
Michele Freeman, MPH
Ana Quiñones, PhD

EXECUTIVE SUMMARY

BACKGROUND

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in the developed world. In 2004, AMD affected 1.75 million persons in the United States, a number that is expected to rise to nearly 3 million by 2020 due to the aging of the population.

The severity of macular degeneration ranges from Category 1 (least severe) to Category 4 (most severe), and "advanced AMD" is defined as having geographic atrophy involving the center of the macula or features of choroidal neovascularization.

Observational studies suggest that people with dietary intakes higher in various carotenoids, antioxidants and omega-3 fatty acids have a lower risk of developing AMD. This has led to several supplementation trials designed to examine the ability of nutritional supplement with carotenoids, antioxidants, or omega-3 fatty acids to prevent the progression of AMD.

Our report focuses on the evidence documenting the potential benefits and harms of certain dietary supplements in patients with AMD. We conducted a systematic review of published literature to address the following key questions:

1) In patients with age-related macular degeneration, do nutritional supplements containing carotenoids, antioxidants, or omega-3 fatty acids alone or in combination prevent functional visual loss?

2) In adult populations, what are the harms of carotenoid, antioxidant, and omega-3 fatty acid supplementation?

METHODS

We conducted searches in Medline® Embase, Scopus, Conference Papers Index, and the Cochrane Library (Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; Cochrane Central Register of Controlled Trials) from 1947 or database inception through February 2011. We obtained additional articles from systematic reviews, reference lists of pertinent studies, reviews, editorials, and by consulting experts. Reviewers trained in the critical analysis of literature assessed for relevance the abstracts of citations identified from literature searches. Full-text articles of potentially relevant abstracts were retrieved for further review. We assessed the internal validity of each study using the Cochrane Risk of Bias tool. We assessed the overall quality of the body of evidence for each outcome by considering the consistency, coherence, and applicability across studies, as well as the internal validity of individual studies, using a method developed by the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group. We critically analyzed the evidence on efficacy and adverse effects, and compiled a narrative synthesis of findings.

RESULTS

We reviewed 4,335 titles and abstracts from the electronic search, and identified 22 additional references through manual searching of reference lists or from input from technical advisors.

After applying inclusion/exclusion criteria at the abstract level, 347 full-text articles were reviewed. Of the full-text articles, we rejected 308 that did not meet our inclusion criteria.

Key Question #1. In patients with age-related macular degeneration, do nutritional supplements containing carotenoids, antioxidants, or omega-3 fatty acids alone or in combination prevent functional visual loss?

We identified seven randomized controlled trials (RCTs) of nutritional supplements in AMD patients. A significant effect in preventing functional loss was found only in the two largest trials. The weight of evidence was dominated by the Age Related Eye Disease Study (AREDS) in terms of sample size (N=3640) and duration of follow-up (7 years). The sample sizes in the other six studies ranged from 60 to 164 subjects, with follow-up ranging from 6 to 24 months. Given that progression of AMD occurs slowly and with low frequency, the smaller studies might have been of insufficient duration or power to detect a treatment effect.

In the AREDS study, a beneficial effect was observed with a combination of antioxidants (500 mg vitamin C, 400 IU vitamin E, and 15 mg beta carotene) plus zinc (80 mg zinc oxide and 2 mg cupric oxide) but only among subjects with Categories 3 and 4 AMD. No significant change was reported in mild AMD subjects (Category 1 or 2) in any of the three treatment arms (i.e., antioxidants alone; zinc alone; or antioxidants plus zinc) compared with placebo. The protective effect of greatest magnitude among all of the supplement treatment arms was noted in the zinc plus antioxidant group (OR 0.63, 99% CI 0.44-0.92).

Key Question #2. In adult populations, what are the harms of carotenoid, antioxidant, and omega-3 fatty acid supplementation?

Vitamin E at high doses (>=400 IU/day) may be associated with increased risk of mortality, congestive heart failure, and prostate cancer.

Beta-carotene may be associated with an increased risk of lung cancer among active smokers. In the Beta-Carotene and Retinol Efficacy Trial (CARET) and Alpha-Tocopherol and Beta-Carotene (ATBC) trials, beta-carotene was associated with increased mortality and increased risk of lung cancer among smokers. Two other large trials, the Women's Health Study (WHS) and the Physicians' Health Study (PHS), did not find an excess risk of lung cancer among smokers using beta-carotene, but a meta-analysis combining these four studies determined that the overall risk of lung cancer among current smokers treated with beta-carotene was significantly elevated (OR 1.24 (95% CI, 1.10-1.39)). No increase in lung cancer incidence was observed among former smokers and nonsmokers in these studies. In prospective cohort studies that used lower doses than RCTs, a small inverse association between carotenoids and lung cancer among current smokers has been observed.

Zinc was associated with urinary tract infections and hospital admissions due to genitourinary causes in one study.

Yellowish discoloration of the skin was frequently reported in trials of beta-carotene, and has also been noted in trials of lutein. Gastrointestinal symptoms were also commonly reported in trials of various supplements.

DISCUSSION

We found good evidence mainly from one large RCT (AREDS) that supplementation with carotenoids and antioxidants decreased the risk of functional vision loss among patients with Category 3 or 4 AMD. One smaller RCT also found zinc supplementation may decrease the risk of clinically significant visual loss among patients with Category 3 or 4 AMD. The effects of carotenoids or omega-3 fatty acids alone have not been well-studied. An ongoing study (AREDS II) is currently being conducted to evaluate the effects of carotenoids (lutein and zeaxanthin) and omega-3 fatty acids (DHA and EPA) on AMD progression in approximately 4,200 subjects with Categories 3 to 4 AMD.

In the AREDS trial, there was no detectable effect on vision loss in any of the treatment arms among subjects with Category 1 or 2 AMD, due to the very slow rate of disease progression in these subjects. Based on the findings of AREDS, we estimate that a trial of Category 2 AMD patients would need an approximate sample size of 17,000 subjects, followed for at least five years, to detect a significant difference in functional vision loss associated with supplementation.

Higher doses of vitamin E (>400 IU per day) have been associated with an estimated four percent increase in mortality; a 13 to 17 percent increase in risk of prostate cancer; and a 13 to 50 percent increase in risk of congestive heart failure among those with existing CVD risk factors such as left ventricular dysfunction, diabetes mellitus, recent myocardial infarction, or renal insufficiency. Carotenoids such as beta-carotene have been associated with an estimated 24 percent increase in risk of lung cancer among smokers. Whether the balance of benefits and harms favors supplementation in AMD patients likely depends on the population being considered. There is strong evidence for benefit in patients with more advanced AMD, and in these patients, the very small risk of harm is likely to be outweighed by the potential benefit.

CONCLUSION

Evidence of benefit from supplementation with carotenoids and antioxidants on functional vision loss in patients with AMD is based mainly on the results of one large trial. The observed benefit occurred only among subjects with Category 3 or 4 AMD. There is evidence for a low risk of harm from some nutritional supplements at high doses. As with any clinical intervention, the balance of benefits and harms regarding supplementation in AMD patients depends on the population being considered. Given that AMD patients are older and have additional medical comorbidities, many would be at risk for some of the potential harms associated with supplementation. The precautionary principle should be observed while further evidence evolves.

While our report notes the uncertainty in the conclusions of many of the included studies, reasonable recommendations can be extended:

- Carotenoid and antioxidant supplements significantly decrease visual loss and can be recommended for patients with Categories 3 and 4 AMD.
- Current literature does not support the use of these supplements for patients with mild AMD.
- Certain nutritional supplements have significant potential harms:
    - Increased mortality and congestive heart failure in high risk patients with vitamin E.
    - Increased risk of prostate cancer with vitamin E.
    - Increased risk of lung cancer among smokers with beta-carotene.

The table below summarizes the evidence on the benefits and harms of oral supplements for AMD.

EXECUTIVE SUMMARY TABLE

Summary of the evidence of the effects of nutritional supplements in patients with age-related macular degeneration

Outcome	Treatment	Population	Effect*	GRADE Classification†	Comment
Functional vision loss	Carotenoids	Early AMD	(~)	Low	Single study (N=90) found a small increase in visual acuity after 12 months, but the improvement was not clinically significant (i.e. <15 letters).
	Antioxidants‡	Categories 3-4 AMD	(+)	Moderate	Evidence of benefit from 1 large multicenter trial (AREDS) and 1 smaller trial. 4 small trials found neutral effects on functional vision loss.
	Antioxidants	Category 2 AMD	(~)	Low	No evidence of benefit after 7 years of treatment in 1 large multicenter trial (AREDS) that included 1,063 Category 2 subjects.
	Omega-3 fatty acids	Early AMD (94% in Categories 1- 2)	(~)	Very low	1 study found evidence of slowed visual acuity loss but not to a clinically significant degree. Very few subjects in this study (6.4%) had Categories 3-4 AMD.
Quality of life	Carotenoids	AMD	(~)	Low	No significant findings on night driving in one study (N=90).
	Antioxidants	N/A	(0)	N/A	No evidence.
	Omega-3 fatty acids	N/A	(0)	N/A	No evidence.
Mortality	Beta-carotene	Smokers	(–)	Moderate	High-dose beta-carotene (20 to 30 mg/day) was linked with increased mortality in 2 large trials in smokers and asbestos workers.
	Vitamin E	General population	(–)	High	High-dose vitamin E (>=400 IU/day) was associated with a slight increase in mortality in a meta-analysis of 11 trials.
Lung cancer	Beta-carotene	Smokers	(–)	Moderate	High-dose beta-carotene (20 to 30 mg/day) was linked with increased lung cancer incidence among smokers in a meta-analysis of 4 large trials. No increase in lung cancer was observed among former and non-smokers.
Prostate cancer	Vitamin E	General population	(–)	Low	High-dose vitamin E (400 IU/day) was associated with an increase in prostate cancer in one study.
Gastrointestinal cancers	Antioxidants	General population	(~)	High	Supplements had no effect on incidence of gastrointestinal cancers in a meta-analysis of 12 good-quality trials.

Outcome	Treatment	Population	Effect*	GRADE Classification†	Comment
Congestive heart failure	Vitamin E	DM, CVD, or post-infarction	(–)	Low	Vitamin E (300-400 IU/day) was linked with increased CHF hospitalization in 2 trials of high-risk patients.
Urinary tract infections (UTIs)	Zinc	AMD	(–)	Low	Zinc (80 mg/day) was associated with more UTIs and hospital admissions due to genitourinary causes compared with non-zinc treated subjects in one large study.
Yellowing of the skin	Beta-carotene Lutein	AMD and general population	(–)	High	Transient yellowing of the skin was frequently reported in trials of beta-carotene and in two trials of lutein.
Gastrointestinal (GI) symptoms	Antioxidants	AMD	(–)	High	GI symptoms were the most common adverse effect that led to withdrawal from studies, according to a systematic review of 10 RCTs of antioxidant supplements for AMD.

GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; ICU = intensive care unit; RCT = randomized controlled trial; AMD = age-related macular degeneration; CHF = congestive heart failure.

* Effect: (+) benefit; (–) harm; (~) mixed findings/no effect; (0) no evidence.

† GRADE classification: high = further research is very unlikely to change our confidence on the estimate of effect; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low = any estimate of effect is very uncertain.

‡ Trials of antioxidants included treatment with antioxidants alone or combined with carotenoids or other supplements.