DIETARY INTERVENTIONS FOR AMD: WHAT DO WE KNOW, AND WHAT DO WE NOT KNOW?

Jennifer R Evans[1]

John G Lawrenson[2]

1 International Centre for Eye Health, Clinical Research Department, London School of Hygiene and Tropical Medicine, London, UK

2 Division of Optometry and Visual Science, City University, London UK

Dietary interventions for AMD

Key words: AMD nutrition

This is the first in a series of short articles summarising the results of Cochrane reviews.

Dietary supplements are marketed to people worried about their eyes, and recommended by eye health care professionals for people who have signs of age-related macular degeneration (AMD). But how much do we actually know about which dietary interventions prevent or slow down the progression of AMD? And what do we know about the adverse effects of supplements? This article summarises the Cochrane reviews on nutritional supplementation in AMD.

There are three relevant reviews on *The Cochrane Library* [1-3]. Overall the reviews include a total of 16 trials. Two reviews focus on the role of antioxidant supplementation in the prevention [1] and progression [2] of AMD and one review focuses on the role of omega-3 supplementation [3]. The reviews are slightly different in scope: the antioxidant reviews are restricted to dietary supplements (pills containing vitamin/mineral supplements alone or in combination), the omega-3 review also considers dietary sources, for example, fish consumption. All three reviews focus on intervention studies, specifically experimental studies where participants have been randomly allocated to dietary supplement or placebo/no intervention.

The Cochrane review on antioxidant vitamin and mineral supplements to prevent AMD includes four trials [1]. The searches for trials were last done in January 2012. This review provides high quality evidence that people aged 40 years and above in the general population are unlikely to prevent the development of AMD by taking vitamin E or beta-carotene supplements. By "high quality" evidence, we mean that further research is unlikely to change the conclusions of the review [4]. The included trials were large (enrolling between 1,000 and 40,000 participants), conducted so as to avoid bias, and were consistent with each other. The review does not tell us about the role of commonly marketed multivitamin combinations, nor about the effect of lutein or zeaxanthin supplements on the prevention of AMD. We do not know whether or not the general population should take these multivitamin or lutein/zeaxanthin supplements to prevent the development of AMD in later life.

In contrast, the Cochrane review on antioxidant vitamin and mineral supplements to slow down the progression of AMD (searches done August 2012) includes at least one large trial (AREDS [5]) that found that a multivitamin combination slowed down the progression of AMD [2]. AREDS was large, well-designed and well-reported, and found a statistically significant effect on progression to advanced AMD. People with AMD[1] who took the AREDS formula[2] had a 32% reduced odds (99% confidence intervals (CI) 7% to 51%) of progression to advanced AMD over an average of 6.3 years of follow-up. If we assume that on average approximately 300 in every 1000 people with AMD will experience progression to advanced AMD then this study suggests that fewer people (on average 226 per 1000) will experience such progression if they take the AREDS formula.

The Cochrane review includes a total of 12 other trials. These other trials are smaller and of shorter duration and investigate a heterogenous group of supplements. Overall these smaller trials do not provide evidence of any benefit of supplementation. So although this

[1] AMD was defined as extensive small drusen, intermediate drusen, large drusen, noncentral geographic atrophy, or pigment abnormalities in one or both eyes, or advanced AMD/vision loss due to AMD in one eye

[2] AREDS formula (per day): vitamin C (500g), vitamin E (400 IU), beta-carotene (15mg), zinc oxide (80mg).

review finds some evidence of benefit for people with AMD of supplementation with a specific combination of antioxidant vitamins and zinc, overall the evidence is graded as "moderate". The majority of participants were enrolled in the largest and longest duration trial, which demonstrated a benefit but there were no other published trials investigating the same formulation with which to compare the results. So it is difficult to assess the consistency of this finding with the data available. Further research may change the estimate of effect. This review did not find convincing evidence that lutein and zeaxanthin slowed down the progression of AMD but current included trials (3 trials, 246 participants) were not reported in such a way as to enable their meaningful inclusion in the review. One further trial has since been published and will be included in the next update of the review [6].

The omega-3 review was completed recently; searches were done in April 2012. No eligible trials were identified but there are ongoing trials that will be published in the near future and the review will be updated when data from these trials become available. AREDS2, for example, is investigating the role of lutein/zeaxanthin and omega-3 fatty acids on progression to advanced AMD (http://www.areds2.org/, accessed 29th November 2012).

Although "generally regarded as safe", vitamin and mineral supplements may have harmful effects. In the past few years there have been reports of adverse effects in particular subgroups of the population. Beta-carotene supplementation has been associated with an increased risk of lung cancer in people who smoke or who have been exposed to asbestos [7], vitamin E has been associated with an increased risk of heart failure in people with diabetes [8]. A Cochrane review of vitamin and mineral supplements and mortality concluded "*Beta-carotene and vitamin E seem to increase mortality, and so may higher doses of vitamin A. Antioxidant supplements need to be considered as medicinal products and should undergo sufficient evaluation before marketing*"[9].

The Cochrane reviews do not provide information on the role of diet and the development or progression of AMD. There is a considerable literature on diet and AMD drawn from observational studies, not all of it consistent. The role of diet may be complex, and it may be dietary patterns or healthy lifestyles, rather than individual nutrients that are important [10]. Randomised controlled trials may not be a feasible study design for measuring the effects of diet which means that conclusions will be based on observational studies. This can be problematic because people who choose, or have access to, a relatively high dietary intake of vitamins (or omega-3 fatty acids) differ in many other ways to people who eat less of these nutrients. In addition (as for trials) there may be problems with selective publication of promising results. There is a need for a critical systematic review of the evidence for an association between diet and AMD that includes explicit assessment of the quality of the evidence using the GRADE approach[4] .

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

No competing interests.

JE and JL made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data of the Cochrane reviews on which this summary is based.

JE drafted this summary and JL revised it critically for important intellectual content. Both JE and JL approved the version to be published.

References

1. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. Cochrane database of systematic reviews 2012(6):CD000253 doi: 10.1002/14651858.CD000253.pub3[published Online First: Epub Date]|.
2. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Cochrane database of systematic reviews 2012(11):CD000254 doi: 10.1002/14651858.CD000254.pub3[published Online First: Epub Date]|.
3. Lawrenson JG, Evans JR. Omega 3 fatty acids for preventing or slowing the progression of age-related macular degeneration. Cochrane database of systematic reviews 2012(11):CD010015 doi: 10.1002/14651858.CD010015.pub2[published Online First: Epub Date]|.
4. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj 2008;336(7650):924-6 doi: 10.1136/bmj.39489.470347.AD[published Online First: Epub Date]|.
5. Age-Related Eye Disease Study Research G. 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. Archives of ophthalmology 2001;119(10):1417-36
6. Beatty S, Chakravarthy U, Nolan JM, et al. Secondary Outcomes in a Clinical Trial of Carotenoids with Coantioxidants versus Placebo in Early Age-Related Macular Degeneration. Ophthalmology 2012 doi: 10.1016/j.ophtha.2012.08.040[published Online First: Epub Date]|.
7. Omenn GS. Chemoprevention of lung cancers: lessons from CARET, the beta-carotene and retinol efficacy trial, and prospects for the future. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation 2007;16(3):184-91 doi: 10.1097/01.cej.0000215612.98132.18[published Online First: Epub Date]|.
8. Lonn E, Bosch J, Yusuf S, et al. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. JAMA : the journal of the American Medical Association 2005;293(11):1338-47 doi: 10.1001/jama.293.11.1338[published Online First: Epub Date]|.
9. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane database of systematic reviews 2012(3):CD007176 doi: 10.1002/14651858.CD007176.pub2[published Online First: Epub Date]|.
10. Mares JA, Voland RP, Sondel SA, et al. Healthy lifestyles related to subsequent prevalence of age-related macular degeneration. Archives of ophthalmology 2011;129(4):470-80 doi: 10.1001/archophthalmol.2010.314[published Online First: Epub Date]|.