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Dietary supplements in age-related macular degeneration

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Background

Age-related macular degeneration (AMD) is the leading cause of blindness in the Western World. Although the exact aetiology is unknown, certain risk factors are associated with AMD, including age, sex, diet, nutritional status, smoking, hypertension and genetic markers. Oxidative stress is thought to be a contributing mechanism1 and thus, the role of dietary antioxidants and supplements has received much interest over the past two decades.2

AREDS

The Age Related Eye Disease Study (AREDS) investigated the role of nutritional supplements in the development and progression of AMD and cataract.3 For AMD, participants were categorised into four categories and observed for a mean of 6.3 years. Of the 1,117 category 1 participants (few if any drusen), the risk of progressing to advanced AMD was predicted to be so low and were excluded from the clinical trial.

Thus most information comes from the 3,640 participants in categories 2–4 in which progression of disease could be assessed. Participants in these categories were randomly assigned to four intervention arms:

- Zinc alone (80mg as zinc oxide and 2mg of copper to prevent anaemia)
- Antioxidants alone (500mg vitamin C, 400IU of vitamin E and 15mg of -carotene)
- Zinc + antioxidants
- Placebo

Only 1.3% of participants in category 2 developed advanced AMD during the period of the study and thus the study is of limited power to inform us on the benefit of supplementation in these early cases of AMD. When these category 2 participants are excluded from the analysis then the five-year risk of developing advanced AMD is 28% for the placebo group, 23% for antioxidants alone group, 22% for zinc alone group and 20% for the zinc + antioxidants group. The odds ratio reduction in developing advanced AMD was only statistically significant for the zinc + antioxidants group. The safety profile for the supplements was excellent for the seven years of follow up although there was increased hospital admissions for genitourinary symptoms associated with zinc and self-reported yellowing of the skin with the antioxidants.

Although controversy and criticism has been vocalised against the sub-group analysis used in the AREDS publications, the recommendations of the study remain that patients with intermediate risk of AMD (category 3 – Figure 1) or advanced AMD in one eye (category 4) should take the zinc + antioxidants formulation.4

Recently, the Rotterdam Study reported that above-median dietary intake of all four of these nutrients was associated with a statistically significant 35% reduction in incident AMD risk, even greater than that observed in the AREDS.5

Carotenoids

The carotenoids form a large class of plant pigments of which 34 have been identified in human serum including lutein, zeaxanthin and -carotene. Only lutein and zeaxanthin are found in retinal tissue as macular pigment. As well as possessing potent antioxidant properties they filter out potentially harmful blue light.
Macular pigment declines with age and in post-mortem eyes with AMD there are lower quantities of lutein and zeaxanthin compared to healthy controls.1,6 Both serum levels and macular pigment density can be altered

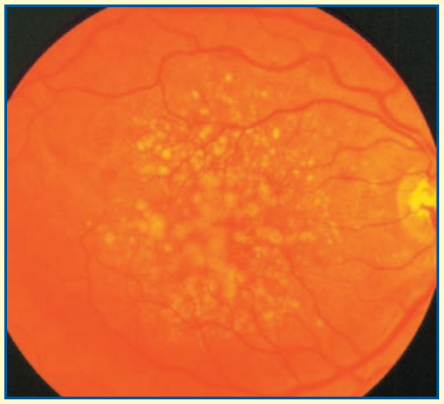

Figure 1: A typical Category 3 (AREDS) fundal appearance showing numerous intermediate and large confluent drusen.

through dietary intake and several epidemiological studies have supported the possible protective role of dietary carotenoids.

In the EDCC study the highest quintile of carotenoid intake was associated with a 43% reduction in risk for AMD. Among the specific carotenoids, lutein and zeaxanthin were most strongly correlated with this reduced risk.7 The Blue Mountain Eye study reported that higher dietary lutein and zeaxanthin intake reduced the risk of incident AMD over 5 and 10 years. Participants in the top tertile of intake (942mg/day) had a decreased risk of incident neovascular AMD (RR 0.35; 95% CI 0.13–0.92), and those with above median intakes (743mg/day) had a reduced risk of indistinct soft or reticular drusen when compared with the remaining population.8

Despite the considerable interest in lutein/zeaxanthin supplementation, high quality RCT evidence is lacking in peer reviewed publications.

The Carotenoids and Co-antioxidants in Age-Related Maculopathy (CARMA) study recruited 433 participants in a well designed, randomised, double masked, prospective trial of lutein and zeaxanthin with co-antioxidants versus placebo. Although the authors conclude there was encouraging improvement for functional and morphological outcomes in high risk participants with carotenoid supplementation the primary endpoint of best corrected distance visual acuity was not met.9

Omega-3 long-chain polyunsaturated fatty acids (LCPUFA)

Omega-3 LCPUFAs include alpha-linolenic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). As they cannot be synthesized by humans de novo they are termed essential fatty acids and diet is their only source. Both alpha-linolenic acid and EPA are dietary precursors to long chain DHA. The major omega-3 fatty acids of interest, DHA and EPA, are found in oily fish, such as tuna, sardines, salmon, and trout.

DHA is present in high concentrations in the outer segments of photoreceptors and its deficiency has been implicated in the development of AMD.10 Several epidemiological studies have suggested an inverse relationship between dietary omega-3 long-chain polyunsaturated fatty acid or fish intake and risk of AMD.

A recent meta-analysis reviewed 9 studies with a total of 88,974 people, including 3,203 AMD cases.11 High dietary intake of omega-3 fatty acids was associated with 38% reduction in the risk of advanced AMD. A minimum fish intake of twice a week was associated with a reduced risk of both early AMD (pooled OR, 0.76; 95% CI, 0.64-0.90) and late AMD (pooled OR, 0.67; 95% CI, 0.53-0.85). The authors concluded that consumption of omega-3 fatty acids may be associated with a lower risk of AMD but that with few prospective studies and no randomised control trials there was insufficient evidence to recommend omega-3 fatty acid supplementation for AMD prevention in the general population.

AREDS2

Several of the controversies surrounding nutritional supplementation in AMD are being addressed by the NEI sponsored AREDS2 study which aims to determine whether oral supplementation with macular xanthophylls (lutein at 10mg/day + zeaxanthin at 2mg/day) and/or omega-3 LCPUFAs, DHA 350mg, and EPA 650mg, will reduce the risk for progression to advanced AMD.

Participants are aged 50–85 years with either bilateral large drusen or large drusen in one eye and advanced AMD in the fellow eye. As the study population in AREDS2 has at least a moderate risk for AMD, all participants will also be offered the original AREDS formulation. A second randomization has been utilized to further refine the AREDS formulation by deleting the use of -carotene and reducing the dosage of zinc to 40mg.

The enrolment of 4,000 participants concluded in June 2008 and we await the five-year follow up data.

Risks/Precautions

The longer term safety profile for the AREDS zinc + antioxidant formula is unknown. Studies using similar doses to the 15mg of -carotene have identified higher incidences of lung carcinoma in smokers.12 Thus AREDS supplements should be avoided in smokers or recent smokers. The Heart Outcomes Prevention Evaluation (HOPE) study found that, among people with vascular disease or diabetes, vitamin E supplementation was associated with a higher risk of heart failure.13 High dose vitamin A supplementation appears to be related to osteoporosis and fractures.14 Fortunately, high levels of serum -carotene appear not to be converted to vitamin A in the body. However, caution must be exercised when using non-AREDS supplements incorporating vitamin A in the retinol form.

Conclusions

The original AREDS formulation provides the best evidence for reduction of incidence of advanced AMD for patients presenting with either large drusen or extensive intermediate drusen (category 3) or advanced AMD in one eye (category 4). The safety profile is good for at least 7 years but should be avoided in smokers or recent ex-smokers. It is tempting to hypothesise, and certainly plausible, that different formulations which may include lutein/zeaxanthin instead of the high doses of -carotene and/or supplementation with LCPUFAs may have additional benefits to those found in AREDS. However, final confirmation of this is awaited in the AREDS2 trial.

At present there is no evidence for the use of nutrient supplements in patients with none or only early signs of AMD. It would be appropriate to advise these patients with regard to the risk of smoking, the benefits of a well balanced diet including fresh fruit, dark green leafy vegetables and oily fish and to be vigilant for the symptoms of developing advanced AMD.

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