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# Age related macular degeneration

## Should your patients be taking additional supplements?

### BACKGROUND

The use of over-the-counter complementary medicines and supplements is growing. Patients with age related macular degeneration (AMD) are likely to have heard of, or are possibly already taking, additional supplements that may increase their chances of retaining useful eyesight.

### OBJECTIVE

This article looks specifically at evidence regarding the effects of over-the-counter oral supplements such as antioxidants and omega-3 fatty acids on AMD.

### DISCUSSION

Diet manipulation and supplementation has a role to play in modifying the risk of disease progression in AMD patients. A combination of vitamins C and E, beta carotene, zinc oxide and cupric oxide has been shown to reduce the rate of visual loss in dry AMD. However, commercially available preparations do not always recommend the correct intake that would match levels found in clinical trials. Other carotenoids such as lutein and zeaxanthin may also be beneficial, intake of these can be increased by altering diet alone. Other useful dietary changes include reducing both animal and vegetable fats and increasing the consumption of fish and nuts.

**Individuals with age related macular degeneration (AMD) represent a large, growing segment of our elderly population. A major finding that has altered management of this condition is the reported beneficial effects of a vitamin/mineral supplement.<sup>1</sup> These supplements are now popularly consumed and actively encouraged by ophthalmologists. Studies have also demonstrated an association between dietary fat intake and the progression of AMD.<sup>2-5</sup>**

### The AREDS

The Age Related Eye Disease Study (AREDS)<sup>6</sup> was a large, American, multicentred, randomised clinical trial that investigated factors influencing the progression of AMD on 4757 participants aged 55–80 years with an average follow up of 6.3 years. The study evaluated the effect of high daily doses of: vitamin C and E, beta-carotene, zinc and cupric oxide (copper). It investigated the effect of taking these supplements in the quantities shown. This precise combination is referred to as the 'AREDS formula':

- vitamin C 500 mg/day
- vitamin E 400 IU/day
- beta carotene 15 mg/day
- zinc oxide 80 mg/day, and
- cupric oxide 2 mg/day.

Patients in the study were healthy, nonsmoking and well nourished compared with the general population. Such patients may not be representative of your patient population.

Results showed a 25% reduction in the loss of visual acuity in those patients randomised to the intervention arm (AREDS formula) of the trial. Benefit occurred in patients with intermediate or advanced AMD, ie. this trial did not study whether or not this formulation could prevent the onset of AMD.

Two carotenoids, lutein and zeaxanthin, were considered for inclusion in the formulation because they are known to be concentrated in the macula.<sup>7</sup> However when the study was commenced, neither carotenoid was readily available. Consequently, beta carotene (another carotenoid) which

**Table 1. Constituents of over-the-counter preparations compared with the original AREDS formula**

Preparation	AREDS formula	Macuvision (1 tablet)	Bioglan Multivision (1 tablet)	Super Vision (1 tablet)	Lutein Vision (1 tablet)	Ocuvite PreserVision (1 tablet)	Cenovis Antioxidant (1 tablet)
Vitamin C	500 mg/day	250 mg/day	250 mg/day	500 mg/day	Nil	113 mg/day	200 mg/day
Vitamin E	400 IU/day	200 IU/day	200 IU/day	Nil	Nil	100 IU/day	150 IU/day
Zinc	80 mg/day	49.8 mg/day	40 mg/day	25 mg/day	Nil	17.4 mg/day	8 mg/day
Cupric oxide	2 mg/day	1.25 mg/day	1 mg/day	Nil	Nil	0.4 mg/day	Nil
Beta carotene	15 mg/day	Nil	Nil	Nil	Nil	4.4 mg/day	6 mg/day
Lutein	Nil	Nil	6 mg/day	Nil	6 mg/day	Nil	Nil

was available, was used in the study.

Although beta carotene was not deemed to be carcinogenic in the population studied, it has been linked with an increased risk of cancer in certain individuals. Studies using similar doses of beta carotene have demonstrated an increased incidence of cancer and mortality in those at high risk for lung cancer (ie. cigarette smokers and asbestos workers).<sup>8-9</sup> Beta carotene should therefore be avoided in current and exsmokers and those who have had previous exposure to other carcinogens which put them at high risk.

#### Specific doses of the components of the AREDS formula

The dose of vitamin C (500 mg/day) used in the formulation is about five times the amount consumed by the general population using diet alone.<sup>10</sup> The 400 IU/day dose of vitamin E is about 13 times the recommended daily allowance (RDA), and the dose of zinc is about five times the RDA. These high levels can generally only be obtained by supplementation.

#### How does the AREDS formula compare to over-the-counter preparations?

Over-the-counter formulations, which contain various amounts of the constituents of the original formulation, are readily available in Australia. As the majority of evidence for the use of this combination comes from the doses used in this trial, a comparison between the original AREDS formula and some of the over-the-counter products is outlined in *Table 1*. None of these formulations exactly matches the AREDS formula. Beta carotene has not been included in most of the formulations because of the link with increased risk of lung cancer in susceptible individuals. Of note, studies

indicating an increased cancer risk with beta carotene used a synthetically derived product. To date, there is no data that has yet made the same associations between cancer and naturally occurring sources of beta carotene (eg. carrots).

Many of the formulations contain antioxidants and zinc doses considerably lower than those previously studied. To obtain doses similar to those studied, most patients need to consume combination supplements (eg. Macuvision or Multivision) each day. However, many of these formulations are advertised as a once per day supplement.

A study conducted by the Department of Ophthalmology in Adelaide (South Australia),<sup>11</sup> found that among 100 patients taking ocular antioxidants and zinc, only 1% were taking the correct dosage. The main conclusion of this study was the need for clinicians to emphasise the recommended dosage, in line with doses already studied.

#### Lutein and zeaxanthin

Lutein and zeaxanthin may be beneficial to macular health<sup>12</sup> but whether they can be substituted for beta carotene was not answered by the original AREDS. Lutein is a plant pigment and zeaxanthin is an isomer of lutein and both belong to the carotenoid family. Lutein and zeaxanthin are not essential dietary components. They are however, the only carotenoids found in the eye. It is hypothesised that they play a role in absorption of blue light, which is damaging to retinal tissues. They may also have a role as antioxidants.

The Lutein Antioxidant Supplementation Trial (LAST)<sup>13</sup> compared the use of lutein supplementation (10 mg/day) with lutein supplementation plus high doses of antioxidants,

vitamins and minerals. These two intervention groups were subsequently compared to a third placebo group. The trial included 90 patients known to have atrophic/dry AMD (86 men) who were followed for 1 year. Approximately a third of patients were assigned to each group. Results showed a significant improvement of the quality of visual acuity in both intervention groups. Patients taking lutein plus additional supplements were found to have the greatest improvement in contrast sensitivity.

Long term risks of lutein are not known, it may therefore be sensible to either rely on dietary intake or advise supplements that reflect a level of lutein that can be obtained by dietary intake. Studies from the USA show an average intake of 1.3 mg/day,<sup>14</sup> however the range of intake was relatively large with 10% consuming >6 mg/day. Although it is possible to obtain >6 mg of lutein per day from diet alone, it competes with other carotenoids for absorption<sup>15</sup> and therefore excess supplementation may lead to reduced absorption of other carotenoids. Given this, and our previous knowledge of potential side effects of other carotenoids, it may be wise to avoid taking high doses until further evidence is available. Taking 6 mg/day, which represents the upper range of what is normally obtained from diet alone, appears to be the sensible choice. For supplements that contain lutein see *Table 1*.

Interestingly one study<sup>16</sup> found that consuming one chicken egg per day for 5 weeks increased serum lutein and zeaxanthin levels by 26 and 38% respectively. Serum concentrations of total cholesterol, LDL, HDL and triglycerides were not adversely affected. This finding implies that lutein and zeaxanthin levels can be significantly increased by altering diet alone

without adverse effects on lipid profile.

Lutein is also found in dark leafy vegetables including spinach, silverbeet and turnip greens, as well as in sweet corn and egg yolks. Half a cup of cooked spinach contains approximately 6 mg of lutein, and one cup of sweet corn provides 2.5 mg.

Combination products containing high dose antioxidants and vitamins combined with lutein are becoming readily available. They do however, usually contain an array of other constituents and therefore need to be chosen carefully.

## Fats

A study investigating the association between fat intake and its relationship with the rate of progression of AMD<sup>17</sup> found that:

- a high intake of both animal and vegetable fat increased the rate of progression of AMD, however results were stronger and more significant for vegetable fat
- a higher intake of saturated, monounsaturated, polyunsaturated, and transunsaturated fats increased the likelihood of progression
- a higher intake of processed, baked goods, which are higher in some of these fats, increased the rate of AMD progression approximately twofold, and
- higher fish intake was associated with a lower risk of AMD progression among subjects with lower linoleic acid intake; nuts were also found to be protective.

## Further research

The AREDS-2 and other trials are continuing to investigate the role of lutein, zeaxanthin and omega-3 in reducing the risk of progression of AMD.

## Resource

The Macular Degeneration Foundation website ([www.mdfoundation.com.au](http://www.mdfoundation.com.au)) is an excellent, informative resource for health care professionals and patients.

Conflict of interest: none declared.

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