Northern Treatment Advisory Group

Dietary Supplements for Treatment of Age-Related Macular Degeneration

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Summary

- Current treatment options for dry AMD are limited, consisting mainly of social support, visual rehabilitation and the provision of aids to help with reduced vision. It has been proposed that a diet rich in antioxidant vitamins or minerals may slow down the progression of AMD. A wide variety of antioxidant vitamin and mineral supplements promoted for the improvement of ocular health are available in the UK. None of these supplements are licensed for the treatment of AMD.

- A number of randomised controlled studies and observational studies of varying quality have examined the efficacy of various vitamin and mineral supplements on the progression of AMD.

- The evidence for the use of high-dose vitamin and mineral supplements in the treatment of AMD is based primarily on the two large randomised controlled trials. In the AREDS study, a specific combination of antioxidant vitamin and mineral supplements (AREDS formulation) demonstrated a modest reduction in the progression to advanced AMD compared to placebo. Supplementation was most beneficial for people who had intermediate or advanced AMD. In AREDS2, the addition of lutein plus zeaxanthin or omega-3 to the AREDS formulation did not provide additional benefit.

- Of the supplements currently available in the UK, the Viteyes® Original or Viteyes 2 formulas would be the preferred options as they are the least expensive preparations that contain the correct combination of vitamins and minerals used in the AREDS studies.

- These products contain significantly higher than recommended daily allowances and their long-term safety is unknown. Hospitalisation for genitourinary problems was more common in people taking zinc supplements and yellowing of the skin was more frequent in people taking antioxidants.

- Products containing beta-carotene may be associated with a higher incidence of lung cancer and people who smoke or are recent ex-smokers should not take supplements contain beta-carotene.

- The number of patients with AMD potentially eligible for treatment with multivitamin and mineral supplements is difficult to reliably estimate. If all patients with early stage AMD, and geographic atrophy were to receive treatment with the Viteyes® Original or Viteyes® 2 supplements this would cost £1,314,000 and £1,849,360 per 100,000 patients aged 50 years and over, respectively. If treatment was restricted only to those with geographic atrophy the annual cost would be £147,825 and £208,053, respectively.
Introduction

Age-related macular degeneration (AMD) is the leading cause of vision impairment in people over 50 years old. It may occur in one or both eyes and causes progressive changes in the macula, the area of the retina responsible for central vision. As peripheral vision is unaffected by AMD it does not result in complete loss of vision.1-5

There are two main types of AMD; dry (atrophic) and wet (neovascular or exudative). Dry AMD, is the most common form and accounts for around 90% of AMD cases. It develops when the retinal tissue thins and becomes atrophic and has three main stages:

- Early - characterised by the presence of several small or a few medium-sized yellow deposits (drusen) beneath the outer layer of the retina known as drusen
- Intermediate - characterised by extensive medium, or one or more large drusen, or geographic atrophy not involving the macula.
- Advanced - in which there is geographical atrophy of the macula.

Dry AMD has few symptoms in the early stages and most cases develop very slowly with a gradual progressive loss of vision. However, approximately 10% of patients with dry AMD will progress to the more severe wet form. Wet AMD is always regarded as an advanced form of AMD and occurs when abnormal blood vessels grow underneath the retina. These fragile vessels leak blood and fluid, resulting in scarring of the retina. It can develop very quickly, leading to severe loss of central vision in a short period of time.1-6

There is no cure for either type of AMD. Only the wet form is currently reversible, with intravitreal therapies targeted at inhibition of vascular endothelial growth factor (VEGF) the treatment of choice. At present, no such therapy exists for dry AMD, with treatment consisting mainly of social support, visual rehabilitation and the provision of aids to help with reduced vision. Reducing the number of people registering as severely visually impaired as a result of AMD is an objective in the Public health outcomes framework for England.1-8

AMD affects more men than women and is most common in people over 50 years with risk increasing significantly with age. It is estimated that 10% of people over 65 have some degree of AMD. In the UK by 2015, it is estimated that 1,661,499 people will have early stage disease, and geographic atrophy will be present in 212,627 people.2,4,9

The exact aetiology of AMD is unknown, though cumulative oxidative damage to the retina is considered to be a key contributory factor. It has been proposed that a diet rich in antioxidant vitamins or minerals may slow down the progression of AMD. This report will review the efficacy, safety and potential cost of using antioxidant vitamin and mineral supplementation in people with AMD.1,2,5,6,10
Clinical evidence

A number of randomised controlled studies and observational studies of varying quality have examined the efficacy of various vitamin and mineral supplements on the progression of AMD.

AREDS\textsuperscript{11}

The Age-Related Eye Disease Study (AREDS) was a randomised, double-blind, multi-centre trial designed to evaluate the efficacy of antioxidants and/or zinc supplements on the progression of AMD and vision loss.\textsuperscript{11} The study was funded by the National Eye Institute (NEI), one of the US government's National Institutes of Health. A total of 3,640 subjects aged 55 to 80 years were enrolled in one of three AMD categories:

- Category 2: Early or borderline AMD, in one or both eyes.
- Category 3: Intermediate AMD, in one or both eyes.
- Category 4: Advanced AMD (dry or wet form), in one eye only.

Subjects were randomly assigned to one of four treatment arms and received an oral daily supplement containing either: (a) antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg); (b) zinc, 80 mg as zinc oxide and copper, 2 mg as cupric oxide to prevent potential anaemia; (c) antioxidants plus zinc; or (d) placebo. The co-primary outcomes were: progression to advanced AMD, and reduction in visual acuity (≤15-letter decrease).

Median follow-up was 6.3 years, with 2.4% of subjects lost to follow-up. In the primary analyses of all participants in categories 2, 3 and 4, the combination of the antioxidant vitamins plus zinc demonstrated a statistically significant reduction in the progression to advanced AMD compared to placebo (odds ratio, 0.72; 99% CI, 0.52–0.98; \( P = 0.002 \)). There was no statistically significant difference for antioxidants alone or zinc alone or compared to placebo (OR 0.80 [0.59 to 1.09], and (OR 0.75 [0.55 to 1.03]), respectively. In category 2 participants, only 15 AMD events occurred after five years and these were evenly distributed across all four treatment arms (3 in the placebo group). With such a low event rate the investigators considered it impossible to assess the treatment effect on the progression to advanced AMD in this group of patients. Therefore, a secondary analysis was conducted using only participants with more severe disease (categories 3 and 4, \( n = 2,556 \)). This analysis showed a greater reduction in risk of progression of AMD (antioxidants plus zinc: OR 0.66 [0.47 to 0.91], \( P = 0.001 \); zinc alone OR 0.71 [0.52 to 0.99], \( P = 0.008 \); and antioxidants alone OR 0.76 [0.55 to 1.05]). However, these results must be interpreted cautiously as the study was not powered for this analysis.

With respect to the rates of visual acuity loss the only statistically significant reduction occurred in patients in categories 3 and 4 assigned to receive antioxidants plus zinc (OR 0.73 [99% CI 0.54 to 0.99]. Again this analysis was underpowered. This treatment effect appeared to be maintained in participants during an additional five years follow-up.\textsuperscript{12}
**AREDSS**

AREDSS was a randomized, double-blind, multi-centre trial designed to assess whether the inclusion of lutein plus zeaxanthin, and/or omega-3 fatty acids to the original AREDS formulation would reduce the progression to advanced AMD. The study also aimed to investigate the effects of removing beta carotene and/or lowering the level of zinc from the original AREDS formulation. The study was funded by the NEI. The primary analysis was conducted in 4,203 subjects, aged 55 to 80 years, who had intermediate AMD or large drusen in one eye and advanced AMD in the other eye. Subjects were randomly assigned to one of four treatment arms and received an oral daily supplement containing either: (a) lutein (10 mg) plus zeaxanthin (2 mg); (b) omega-3 fatty acids (docosahexaenoic acid [DHA] plus eicosapentaenoic acid [EPA]); (c) both lutein/zeaxanthin and DHA/EPA; or (d) placebo. In addition, all participants received either the original AREDS formulation or accepted a secondary randomisation to receive one of four variations of the AREDS formulation. The primary outcome was development of advanced AMD.

Median follow-up was 4.9 years, with 3% of subjects lost to follow-up. In the primary analyses comparison with placebo demonstrated no statistically significant reduction in progression to advanced AMD (hazard ratio, 0.90 [98.7% CI, 0.76 -1.07]; for lutein plus zeaxanthin; HR 0.97 [0.82 - 1.16]; for DHA/EPA; HR 0.89 [98.7% CI, 0.75-1.06]; for lutein/ zeaxanthin and DHA/EPA), respectively. The analyses were performed with stratification by secondary interventions. The analyses conducted without secondary intervention stratification were comparable to these results.

Of the 4,203 participants, 3,036 agreed to a secondary randomisation and received an oral daily supplement containing either: (a) the original AREDS formulation; (b) the AREDS formulation minus beta carotene; (c) the AREDS formulation with low zinc (25 mg); or (d) the AREDS formulation minus beta carotene and including low zinc. Due to potential concerns regarding an increased risk of lung cancer with beta carotene supplements, current smokers and those who had stopped smoking within one year prior to randomisation were assigned to one of the two arms that excluded beta carotene. Results of this analyses showed that lowering zinc dose and eliminating beta carotene had no statistically significant effect on progression to advanced AMD (HR, 1.06 [0.95 -1.19] and 1.07 [0.94 – 1.20], respectively.

**VECAT**

The vitamin E, Cataract and Age-related maculopathy trial [VECAT] investigated whether vitamin E supplementation educed the incidence or progression of cataract and AMD. A total of 1,204 participants aged 55 to 80 years were randomised to vitamin E (500 IU daily) or placebo and followed four years. Over 80% of participants in this study did not have signs of AMD. The primary outcome was development of AMD and secondary outcomes were the progression of AMD and changes in visual acuity.
Dietary supplements to slow AMD progression

No significant difference was found in the progression AMD between the vitamin E and placebo groups either by photographic- or clinical grading (OR 1.11, [0.81 – 1.53]) and (OR 1.33, [0.82 – 2.16]), respectively. Similarly, there was no evidence of any treatment effect on visual acuity (OR 1.05, 95% CI [0.71 – 1.54]).

Other published studies

The other published trials of multivitamin or mineral supplements have a number of limitations, including problems of data collection, inadequately defined outcomes, difficulty in assessing nutrient intake, and inability to control for confounding factors which may account for inconsistencies in results. Due to the relatively low prevalence of AMD, many of these studies were underpowered and of too short a duration to detect any modest protective effect of supplements on the prevention of visual loss or progression of AMD.

Cochrane Review (2012)\textsuperscript{15}

A recent Cochrane review of antioxidant vitamin and mineral supplements for slowing the progression of AMD included thirteen randomised trials. Over half of the subjects included in the review were derived from the original AREDS study. Based on the findings of the AREDS study the review concluded that people with AMD may experience delay in progression of the disease with antioxidant vitamin and mineral supplementation. The other smaller trials with shorter follow-up do not provide evidence of any benefit.

Safety

Of the studies discussed above, only AREDS has examined the safety of vitamin and mineral supplements in any detail.

In the first AREDS study no statistically significant differences in serious adverse events were noted across the treatment arms.\textsuperscript{11} Participants in the antioxidant groups more frequently reported yellow skin (8.3% vs. 6.0%, \textit{p}=0.008). Participants in the zinc arms reported more anaemic (13.2% vs. 10.2%, \textit{p}=0.004, however, serum haematocrit levels were unchanged. Further follow-up of this cohort found that hospital admissions for genito-urinary disease (benign prostatic hyperplasia/urinary retention urinary tract infection, urinary lithiasis and renal failure) were significantly more frequent in participants taking zinc supplements (11.1% vs. 7.6%, \textit{p}=0.0003).\textsuperscript{16}

No statistically significant differences in serious adverse events were noted across the treatment groups in AREDS2.\textsuperscript{13} However, in the secondary randomisation which excluded smokers who were smokers significantly more lung cancers were reported in the beta carotene group vs. the no beta carotene group (2.3% vs. 0.9%, \textit{p}=0.04). Ninety one percent of those who developed lung cancer were previous smokers. Supplementation with lutein plus zeaxanthin, DHA/EPA, zinc, or beta carotene had no statically significant effect on overall mortality.

The safety of some of the components of the AREDS supplements has been questioned in other studies. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study found that after a follow-up period averaging 6 years, the
incidence of lung cancer was 16 percent higher among participants who smoked.\textsuperscript{17} This finding was supported in the Beta-Carotene and Retinol Efficacy Trial (CARET).\textsuperscript{18} For this reason, beta-carotene is contraindicated in smokers or those who have been exposed to asbestos. How long people should refrain from taking beta-carotene after smoking cessation remains to be established.

\textbf{Cost analysis}

A wide variety of antioxidant vitamin and mineral supplements promoted for the improvement of ocular health are readily available for purchase without prescription in the UK. All of these supplements are not licensed medicinal products and so they have not undergone regulatory assessment.

\textbf{AREDS original formulation}

Two products are available that exactly or closely match the combination of antioxidants and minerals used in the original AREDS formulation (table 1). The Viteyes\textsuperscript{®} Original formula would be the preferred option as it is the least expensive preparation (annual cost per patient £164.25) that contains the correct combination of vitamins and zinc. However, both contain beta carotene and are therefore not suitable for smokers or recent ex-smokers. A number of similar formulations are available in which beta carotene has been substituted with lutein, but these formulations lack the evidence base of the original AREDS formulation. Some chemists and health food retailers may have own brand products with similar constituents but different proportions of each, use different zinc salts, or contain additional ingredients.

Table 1. Products available in the UK that exactly or most closely match the formula used in the original AREDS study.

<table>
<thead>
<tr>
<th>AREDS\textsuperscript{®} formulation</th>
<th>Viteyes\textsuperscript{®} Original</th>
<th>PreserVision\textsuperscript{®} Original</th>
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<tr>
<td></td>
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</table>

Northern Treatment Advisory Group, May 2014
The prices quoted are retail prices including VAT and are for illustrative purposes only (butterflies Healthcare Ltd). Some of these products may be available from other retailers at slightly reduced costs.

**AREDS2 formulation**

Table 2 shows some supplements currently available in the UK that exactly or most closely match the combination of antioxidants and minerals used in the AREDS2 study. The Viteyes® 2 formula would be the preferred option as it is the least expensive preparation (annual cost per patient £231.17) that contains the correct combination of vitamins and zinc. This product can be given to previous or current smokers as it no longer contains beta-carotene. Some chemists and health food retailers may have own brand products with similar constituents at a lower cost.

The number of patients with AMD potentially eligible for treatment with multivitamin and mineral supplements is difficult to reliably estimate. The AREDS study showed that a specific combination of high-dose vitamin and mineral supplements may slow progression of AMD in people with early to advanced disease. From the RNIB epidemiology model, it is estimated that in the UK by 2015, a total of 1,661,499 people will have early stage AMD (defined as presence of indistinct soft drusen and/or pigmentary abnormalities, but no signs of advanced AMD (wet or dry)), and 212,627 people will have geographic atrophy.

The number of patients with AMD potentially eligible for treatment with multivitamin and mineral supplements is difficult to reliably estimate. The AREDS study showed that a specific combination of high-dose vitamin and mineral supplements may slow progression of AMD in people with early to advanced disease. From the RNIB epidemiology model, it is estimated that in the UK by 2015, a total of 1,661,499 people will have early stage AMD (defined as presence of indistinct soft drusen and/or pigmentary abnormalities, but no signs of advanced AMD (wet or dry)), and 212,627 people will have geographic atrophy. In total, this equates to a prevalence of 8.0%, based on a projected UK population of 23,441,882 aged 50 years and over considered to be at risk of AMD.
Based on a prevalence of 8.0%, if all patients with early stage AMD, and geographic atrophy received treatment with Viteyes® Original this would result in an annual cost of £1,314,000 per 100,000 patients aged 50 years and over. If all patients received Viteyes® 2 this would result in an annual cost of £1,849,360 per 100,000 patients aged 50 years and over. However, the AREDS study showed that the formulation was most beneficial for people who had intermediate or advanced AMD. If treatment was restricted only to those with geographic atrophy (estimated prevalence 0.9%) the annual cost per 100,000 patients aged 50 years and over would be £147,825 and £208,053, respectively.
Table 2. Products available in the UK that exactly or most closely match the formula used in the AREDS2 study.

<table>
<thead>
<tr>
<th>AREDS2® formulation</th>
<th>Viteyes® 2</th>
<th>Viteyes® 2 Advanced</th>
<th>Viteyes® 2 plus Omega 3</th>
<th>EyeBar®</th>
<th>MacuLEH®</th>
<th>Macusheild® Gold</th>
</tr>
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<tbody>
<tr>
<td>Vitamin C</td>
<td>500 mg ✔</td>
<td>500 mg ✔</td>
<td>500 mg ✔</td>
<td>500 mg ✔</td>
<td>500 mg ✔</td>
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<tr>
<td>Vitamin E</td>
<td>400 IU ✔</td>
<td>400 IU ✔</td>
<td>400 IU ✔</td>
<td>400 IU ✔</td>
<td>400 IU ✔</td>
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<tr>
<td>Lutein</td>
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<td>10 mg ✔</td>
<td>10 mg ✔</td>
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<tr>
<td>Zeaxanthin</td>
<td>2 mg ✔</td>
<td>2 mg ✔</td>
<td>2 mg ✔</td>
<td>2 mg ✔</td>
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<tr>
<td>Zinc</td>
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<td>25 mg ✔</td>
<td>25 mg ✔</td>
<td>25 mg ✔</td>
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<tr>
<td>Copper</td>
<td>2 mg ✔</td>
<td>2 mg ✔</td>
<td>2 mg ✔</td>
<td>1.6 mg ✗</td>
<td>2 mg ✔</td>
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<td>Other carotenoids</td>
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<td>none ✔</td>
<td>none ✔</td>
<td>meso-zeaxanthin ✗</td>
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<tr>
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<td>mixed ✗</td>
<td>Omega 3 ✗</td>
<td>none ✔</td>
<td>mixed ✗</td>
<td>meso-zeaxanthin ✗</td>
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<tr>
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<td>Capsules</td>
<td>soft gels</td>
<td>bars</td>
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<td>soft gels</td>
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<td>Pack size</td>
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<tr>
<td>Cost for 28 days supply</td>
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<td>£18.66</td>
<td>£37.33</td>
<td>£27.99</td>
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</tr>
</tbody>
</table>

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Points to consider

The evidence for the use of high-dose vitamin and mineral supplements in the prevention and progression of AMD is based primarily on the two large randomised controlled trials. In the original AREDS study, a specific combination of antioxidant vitamins plus zinc demonstrated a modest reduction in the progression to advanced AMD compared to placebo. The study showed that supplementation was most beneficial for people who had intermediate or advanced AMD.

AREDS2 found the addition of lutein plus zeaxanthin or omega-3 long fatty acids, to the original AREDS formulation did not further reduce risk of progression to advanced AMD.

A wide variety of antioxidant vitamin and mineral supplements promoted for the improvement of ocular health are readily available for purchase without prescription in the UK. All of these supplements are not licensed medicinal products and so they have not undergone regulatory assessment.

Of the supplements currently available in the UK that exactly or most closely match the combination of antioxidants and minerals used in the AREDS studies the Viteyes® Original or Viteyes 2 formulas would be the preferred options as they are the least expensive preparations that contains the correct combination of vitamins and minerals.

These products contain significantly higher than recommended daily allowances and their long-term safety is unknown. Two large randomised controlled trials have suggested that products containing beta-carotene may be associated with a higher incidence of lung cancer in smokers. The original AREDS supplements contain beta-carotene and people who smoke or are recent ex-smokers should not take them.

A healthy diet containing a wide variety of fresh fruit and vegetables is likely to provide many benefits, without any potential harmful effects. However, diet alone will not provide the same high levels of the vitamins and minerals found in the AREDS formulation. It is important to note that participants in the AREDS studies were well nourished with an above average intake of dietary nutrients.

The number of patients with AMD potentially eligible for treatment with multivitamin and mineral supplements is difficult to reliably estimate. Based on the RNIB projections, it is estimated that in the UK by 2015, the prevalence of early AMD and geographic atrophy in people aged 50 years and over will be 8.0%

If all patients with early stage AMD, and geographic atrophy were to receive treatment with the Viteyes® Original or Viteyes® 2 supplements this would cost £1,314,000 and £1,849,360 per 100,000 patients aged 50 years and over, respectively. If treatment was restricted only to those with geographic atrophy the annual cost would be £147,825 and £208,053, respectively.
**Author’s declaration.** The lead author has no relevant interests to declare.

**References**

1. The Royal College of Ophthalmologists. Age-related macular degeneration guidelines for management. September 2013. [www.rcophth.ac.uk](http://www.rcophth.ac.uk).
2. The Royal College of Ophthalmologists. Commissioning contemporary AMD services: A guide for commissioners and clinicians. November 2013 [www.rcophth.ac.uk](http://www.rcophth.ac.uk/).