An ageing population has raised the priority of reducing the risk for age-related eye diseases which impair sight and quality of life. Chief among these diseases is age-related macular degeneration (AMD) – the leading cause of visual impairment among older adults.\(^1\,^2\) There is growing evidence which suggests that nutrition can attenuate the risk and/or progression of age-related macular degeneration. It is, therefore, important that eye professionals are aware of good nutrition for eye health and are able to help patients with dietary modification and supplement choice. This article discusses the latest research, as well as the risks and benefits, of dietary supplements.

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**Learning objectives**

- Understand the risk factors for AMD (Group 6.1.1)
- Understand the latest research on AMD and nutrition.
- Be aware of the dietary supplements available for AMD, their efficacy and any potential contraindications (Group 6.1.9)

- Understand the latest research on AMD and nutrition.
- Be aware of the dietary supplements available for AMD, their efficacy and any potential contraindications (Group 1.1.2)
- Understand the risks and benefits of taking nutritional supplements for AMD (Group 2.1.8)

- Understand the latest research on AMD and nutrition. Be aware of the dietary supplements available for AMD, their efficacy and any potential contraindications (Group 8.1.3)

**About the author**

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Pathology
In the early stages of AMD, a deposition of metabolic pigment debris accumulates between the retinal pigment epithelium (RPE) and Bruch's membrane. These lipid deposits located on the inner collagen layer of Bruch's membrane are clinically visible as pale yellow spots known as drusen.\(^3,4\) In the later stages of the disease, the RPE may atrophy completely. Atrophy can occur in small focal areas or can be widespread. This form of the disease is known as ‘dry AMD’ or ‘geographic atrophy’. In some cases, new blood vessels grow under the RPE and occasionally into the subretinal space. This is known as ‘wet’ or ‘neovascular’ AMD.\(^5\) Haemorrhage can also occur, which often results in increased scarring of the retina. The early stages of the disease are in general asymptomatic. In the later stages there may be considerable distortion within the central visual field, leading to a complete loss of central visual function.

Risk factors
Geographic atrophy or dry AMD is the most common form, and is estimated to be present in 15% of eyes by the age of 80.\(^6,7,8\) Progression is slow and legal blindness has been estimated to occur somewhere between five and 10 years.\(^9\) Neovascular AMD is less common, occurring in 5.2% of the population aged over 75, but accounts for 90% of blind registrations.\(^1,10\) The paucity of treatment options has prompted interest in the identification of risk factors, as well as the development of prevention strategies. The three main risk factors are increasing age, smoking and genetic predisposition, although other proposed factors include gender, race, socioeconomic factors, cardiovascular disease and poor nutrition.\(^1,11-25\)

Nutrition
The lack of effective treatment modalities, coupled with evidence supporting an oxidative pathogenesis, has increased interest in the potential preventative role of nutritional supplementation. There have been many large and small scale trials which have investigated the link between nutrition and AMD and have yielded positive results. Nutrients associated with AMD include antioxidant vitamins C and E, the vitamin A precursor beta-carotene, the xanthophylls lutein and zeaxanthin, omega-3 fatty acids DHA and EPA, zinc, some B vitamins (folic acid, B6, and B12), and other phytochemicals such as anthocyanins, gingko and saffron.

The largest trial to investigate the link between antioxidant vitamins and AMD was the Age-Related Eye Disease Study (AREDS) in 1992. It reported that people with the intermediate stage of dry AMD had a 25% reduction in the risk of developing advanced AMD after taking a supplement which contained beta-carotene 15mg, vitamin C 500mg, vitamin E 400IU, zinc 80mg and copper 2mg. The small amount of copper was added as high doses of zinc can reduce the levels of copper in the body.\(^26\)

However, AREDS1 showed that 7.5% of patients had an increased risk of hospital admission due to bladder/kidney complications from the high doses of zinc.\(^26\) Other research has found that smokers who take high doses of beta-carotene may be at an increased risk of developing lung cancer.\(^27,28\) In people with heart disease or diabetes, taking high dose vitamin E supplements may also increase their risk of heart failure.\(^29\)

The AREDIS2 trial investigated whether the effectiveness of the formula could be improved by reducing the amount of zinc and removing beta-carotene (OT cover story, July 12, 2013). It also had the additional goal of assessing the effects of lutein, zeaxanthin and omega 3 fatty acid on AMD.\(^30\)

Xanthophylls – lutein and zeaxanthin
The dietary xanthophylls lutein (L) and zeaxanthin (Z) may be more effective than other nutrients in reducing AMD risk or progression due to their antioxidant and photo protective properties.\(^31\) The plausibility for this hypothesis is due to the high concentration of L, Z, and a related compound, meso-zeaxanthin (MZ), in the macula, particularly in the fovea, where they are known as the macular pigment (MP).\(^32\) The protective properties of the MP are well established and include the ability to interact with free radicals, prevent lipid peroxidation and filter out high energy, blue light.\(^33,34,35\) Free radicals induce apoptosis of the macular photoreceptors. However, L has been shown to scavenge the oxygen intermediate and quench singlet oxygen (a potent oxidant).\(^6\) MZ has also been shown to decrease lipofuscin which may contribute to drusen formation cultured RPE cells.\(^7,8\)

L and Z are obtained by the human body exclusively from dietary sources, and MZ is converted from L in the macula.\(^12,\)\(^13,24,27\) Therefore an individual’s macular pigment optical density (MPOD) can vary, depending on diet and lifestyle. It has been reported that around 78% of dietary L and Z is obtained from vegetables, with the highest concentrations being found in dark green leafy vegetables, such as kale, turnip greens, collard greens and spinach.\(^12\) A large body of evidence suggests that doses of 10mg/day of L are associated with the most positive effects on MPOD.\(^36,42\) Other factors which may influence MP include smoking habits (lower levels in smokers), iris colour (lower levels with lighter iris colour), gender (higher levels reported in men in some studies) and body

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fat (lower levels in those with a high percentage of adipose tissue). Higher MPOD due to supplementation with L and Z has been correlated with a delay in progression or onset of AMD in some, but not all, epidemiological and intervention studies, and therefore on-going research into its role is important. AREDS2 was a large-scale randomised controlled trial designed to evaluate the effect of supplemental L, Z and omega 3 in respect to the progression to advanced AMD. It found that, overall, there was no additional benefit of adding 10mg of L and 2mg of Z to the original AREDS formula of antioxidants. However, participants who took the AREDS formulation with no beta-carotene, but with L and Z at these doses, had their risk of progression to advanced AMD reduced by 18% compared to those participants who took the AREDS formulation which contained beta-carotene without L and Z. In addition, participants who had a low dietary intake of L and Z at the start of the study, were 25% less likely to develop advanced AMD, compared with participants with similar dietary intake who did not take L and Z. There was no benefit from L and Z supplementation to those who consumed ≥1.030mg of L and Z per day in their diet.

Investigators have suggested that beta-carotene may have masked the effects of L and Z in the overall analysis because it competes with them for absorption in the body. Participants who took beta-carotene and L and Z had lower blood levels of both compared with those who only took L and Z. The investigators also found that former smokers – who made up approximately half of the study population – were at greater risk of developing lung cancer if they took the formula which contained beta-carotene. This means it is likely to be safer for anybody who has ever smoked not to take supplements which contain beta-carotene. It is now suggested that 10mg of L and 2mg of Z are a safe and effective tool for the treatment of AMD as a combination with the original AREDS supplement, without beta-carotene.

Omega 3
The long-chain polyunsaturated omega-3 fatty acids, particularly DHA, are found in high concentrations in the retina where they are important structural components of vascular tissue and rod and cone photoreceptors. The critical role of DHA in normal retinal function is well documented in animals and humans, where it appears to influence cell membrane integrity and permeability, modulates the activity of enzymes and receptors on the membrane, and acts as a precursor for the synthesis of other important biological molecules. Long-chain omega-3 fatty acids, predominantly found in oily fish, may also protect against oxidative damage, and help modulate retinal cell gene expression, cell differentiation and cell survival.

Observational studies suggest that omega-3 poly-unsaturated fatty acids (PUFA) are protective in the eye. A 2008 meta-analysis of epidemiological studies reported that a high intake of omega-3 fatty acids and fish intake at least twice a week may reduce the primary risk of both early and late AMD by up to 38%. Other studies have found similar findings. Some prospective studies also reveal a decreased likelihood of AMD progression in those with early AMD.

However, primary, secondary and subgroup analyses from the AREDS2 trial demonstrated no additional benefit on the reduced risk of progression to advanced AMD by adding the omega 3 fatty acids EPA and DHA to the original formulation. The doses used (DHA 650mg and EPA 350mg) were also found to exhibit no adverse effects after five years of follow-up. These null results may mean that omega 3 is simply an ineffective treatment option for AMD, or it could be related to an inadequate dose, inadequate duration of treatment, or both.

Omega 3 supplements containing the doses used in the AREDS2 trial may not be recommended for AMD patients. However, it is still essential that adequate amounts are met through diet alone as they have...
important cardiovascular health benefits. The Department of Health recommends consuming one or two portions of oily fish per week.

**Zinc**

Low levels of zinc are thought to play a role in the development of AMD. Firstly, zinc is highly concentrated in ocular tissues, particularly in the retinal pigment epithelium, and retinal zinc levels have been shown to decline with age.24-60 Thus, it is hypothesised that zinc supplementation may aid retinal health. The evidence which suggests a link between zinc and AMD comes mostly from the AREDS1 and AREDS2 trials.

There have been no randomised or case controlled investigations involving zinc and the risk of AMD. However, other prospective data has demonstrated some positive results. A small number of cohort studies assessing dietary intakes of zinc in elderly people has found an inverse relationship between high zinc intake and the incidence of early AMD and any stage of AMD.57,58,71 One study also reported a decrease in pigment abnormalities in those with a high consumption of zinc intake from food or supplements.72

In terms of zinc intake and the progression of AMD, a large proportion of the perceived benefit comes from the AREDS1 trial which found a 25% reduction in AMD progression in patients with early AMD using 80mg of zinc, plus other antioxidants, daily. Two smaller sized randomised clinical trials have also found that supplementation with zinc alone improves visual function in patients with AMD. The doses used in the studies were 25mg and 100mg daily. There were little adverse associations in the subject group who received 25mg of zinc.73,74

The negative effects of high zinc supplementation are not fully understood. It is suggested that intakes above the daily recommended values are associated with copper deficiency.75,76 It was also found in the AREDS1 trial that a small number of subjects (7.5%) receiving 80mg per day of zinc suffered with genitourinary infections.26 The AREDS2 trial found that reducing the amount of zinc from 80mg to 25mg does not appear to impact on the effectiveness of the formulation, and a formulation with reduced zinc content is very likely to result in fewer gastrointestinal side effects.

**B vitamins**

Vitamins B6, B12 and folic acid regulate levels of homocysteine in the blood. High levels of homocysteine are a significant risk factor for cardiovascular disease and research suggests that cardiovascular disease and AMD share a similar risk profile. Furthermore, high levels of homocysteine have been found in AMD patients, suggesting an association between elevated serum homocysteine levels and the risk of AMD.77-80 Treatment with folic acid, vitamin B6 and vitamin B12 has been shown to reduce homocysteine levels. In a meta-analysis of randomised controlled trials, folic acid lowered plasma homocysteine levels by 25%, and an addition of B12 lowered levels by a further 7%.8

Further evidence from controlled trials which examine the effect of these nutrients on homocysteine levels in relation to AMD risk or progression is limited, and therefore they cannot be recommended as supplements. Patients, however, can try to include more foods in their diet which contain these nutrients such as whole grains, dairy products, leafy green vegetables, nuts, fish, beef, liver, poultry, potatoes and non-citrus fruits.

**Anthocyanins, gingko and saffron**

There is a small amount of evidence which suggests that some plant pigments, spices and herbs such as anthocyanins found in berries, gingko and saffron may be protective in the eye and beneficial for AMD.57-60 The promising role they play is related to their antioxidant properties and protection from oxidative stress in the retina. However, health professionals should also be aware that convincing evidence of their dosage and efficacy in AMD patients is limited.

**Conclusion**

Overall, there is a great deal of potential for the benefits of taking supplements which contain antioxidant vitamins, L and Z, omega 3 and zinc for the treatment of early stages of AMD, and it is therefore important that people aged between 50 and 85, who present with early signs of the disease are counselled about nutritional supplementation.

AREDS1 and AREDS2 are the largest clinical trials which have taken place in the field of ocular disease and nutrition and it is likely that eye care practitioners will feel more comfortable about recommending the specific combination of nutrients involved in the studies. Results from the AREDS2 trial suggest that taking a combination of 500mg vitamin C, 400 IU vitamin E, 25mg zinc, 2mg copper, 10mg L and 2mg Z may reduce the risk of progression to advanced AMD in people who already have signs of the disease. In this new AREDS formula, beta-carotene has been replaced with L and Z and the high levels of zinc have been reduced.