'What vitamins should I take for my macula, doctor?'

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Patients who are at risk or who have early signs of age-related macular degeneration should take high dose zinc and antioxidants with possible further supplementation with lutein, zeaxanthin, fish oil and selenium if dietary intake of these is inadequate.

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Over the past 12 years the public's awareness of age-related macular degeneration (AMD) has increased from 5% to 85%. Along with this has come an increasing awareness of the importance of diet and nutritional supplements in preventing or slowing disease progression. Increasingly we are being asked, 'what vitamins should I take for my macula, doctor?'

Our advice is driven primarily by the appearance of the early signs of AMD: soft drusen and focal pigment changes in the retina (Figure). Soft drusen are yellow deposits of 125 µm or more in diameter in the macula and indicate a significant risk of progression to 'wet' (i.e. neovascular) or 'dry' (i.e. geographic atrophy) AMD and loss of vision. Patients with these signs are the patients for whom dietary and lifestyle advice and possibly nutritional supplements are important to reduce their risk of losing vision.

Free radical damage – oxidation – plays a major role in the genesis of AMD. All of the dietary and lifestyle advice and the nutritional supplementation shown to be of benefit for patients with AMD can be related to protecting the retina from free radical damage.

DIETARY AND LIFESTYLE ADVICE

General dietary and lifestyle advice to reduce the risk of a person developing macular degeneration and to minimise loss of vision if AMD is present is outlined in Box 1.

Lutein and zeaxanthin are particularly important nutrients for good macular health, and are derived through the diet, mainly from green vegetables. The lutein and zeaxanthin contents of some foods are listed in Table 1. Other nutrients important for macula health and general eye health are zinc, vitamin C, vitamin E and the omega-3 fatty acids.

NUTRITIONAL SUPPLEMENTS

If a person's dietary intake of nutrients for eye health is inadequate, nutritional supplementation may be appropriate. Nutritional supplements that have been shown to be of benefit for macular health are lutein, zeaxanthin and omega-3 fatty acids.

Supplements based on the Age-Related Eye Disease Study (AREDS) formula may be considered by people who have been diagnosed with AMD (Box 2). The original AREDS formula contained beta-carotene but a follow-up study, AREDS 2, revised the formula by removing the beta-carotene and adding lutein and zeaxanthin.

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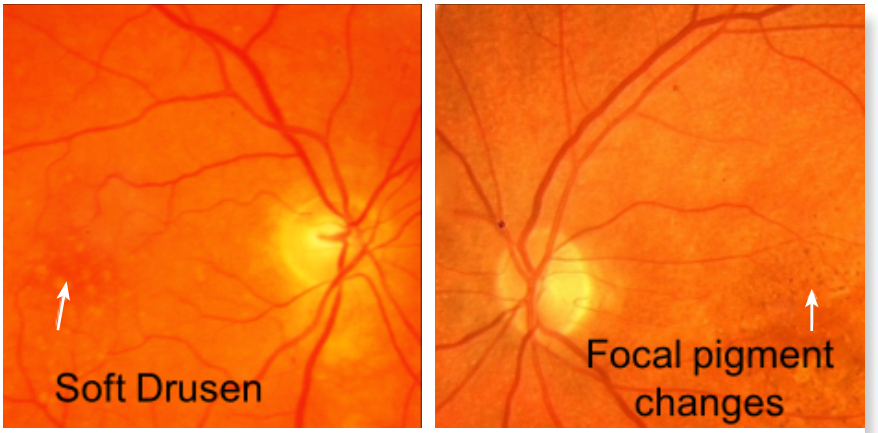

Figure. The early signs of age-related macular degeneration showing soft drusen (left) and focal pigment changes (right).

1. DIET AND LIFESTYLE ADVICE TO MINIMISE EFFECTS OF AMD

- Do not smoke
- Exercise regularly
- Wear sunglasses
- Avoid the seed vegetable oils (i.e. reduce linoleic acid content of diet) by not eating processed baked foods, sauces or margarine. Check bread is not made with vegetable oil
- Eat a handful or more of nuts each week
- Eat lutein-rich food and avoid beta-carotene-rich foods
- Eat chicken rather than red meat
- Use olive oil but avoid olive oil margarine
- Eat low glycaemic index foods

DIETARY NUTRIENTS AND SUPPLEMENT INGREDIENTS

The functions of the various dietary nutrients and components of supplements are listed in Table 2 and discussed in more detail in Box 3 and below.[1-9]

How effective are high dose zinc and antioxidants? Level 1 evidence

A prospective trial by Newsome's group showed that daily high dose zinc (71 mg of elemental zinc) significantly reduced the rate of vision loss in patients with AMD over one to two years.[10]

In 2001, the Age-Related Eye Disease Study (AREDS), a large (n= 4757) multicentre prospective trial over six years, used 80 mg of elemental zinc.[11] This study confirmed that daily zinc alone was effective in slowing the progression of the disease by 20%, and that zinc with the addition of the antioxidants vitamin E 400 IU, vitamin C 500 mg and beta-carotene 15 mg had an additional beneficial effect and reduced the rate of progression by some 25 to 30%. A 10-year follow-up study of participants showed the beneficial effects of the AREDS formula appear to be substantial in the long term.[12] At 10 years, patients initially in AMD category 4 and originally allocated to antioxidant plus zinc had a 56% reduced odds of neovascular AMD ($p<0.001$). Primary allocation to zinc alone was associated with a significantly reduced mortality.

The large (n=4203) multicentre six-year prospective follow-up study to AREDS – AREDS 2 – was carried out with one of its aims being to see if reducing the dose of zinc would affect safety and efficacy compared with the high dose zinc used in

TABLE 1. LUTEIN AND ZEAXANTHIN CONTENT OF FOOD (APPROXIMATE)

Food	Amount	Lutein/zeaxanthin content
Kale, cooked	Half cup	12 mg
Spinach, cooked	Half cup (65 g)	10 mg
Silverbeet, cooked	Half cup	10 mg
Spinach, raw	One cup (30 g)	4 mg
Parsley	Half cup	4 mg
Peas	Half cup	2 mg
Broccoli	Half cup	1 mg
Cos lettuce	One cup	1.3 mg
Iceberg lettuce	–	0
Corn	Half cup	0.6 mg
Asparagus	One serving	1 mg
Zucchini	One serving	1 mg
Green beans	One serving	0.3 mg
Brussel sprouts	One serving	0.2 mg
Avocado	Half cup	0.3 mg
Egg	One	0.25 mg
Cabbage	–	0
Carrot	–	0
Apricot	–	0

2. THE AREDS FORMULA*

- Zinc (as zinc oxide), 80 mg
- Vitamin C, 500 mg
- Vitamin E, 400 IU
- Copper (as cupric oxide), 2 mg

ABBREVIATION: AREDS = Age-Related Eye Disease Study.

* This is the currently used AREDS formula. Beta-carotene was contained in the original AREDS formula. AREDS 2 confirmed the importance of its removal.

TABLE 2. FUNCTIONS OF COMPONENTS OF MACULAR DEGENERATION SUPPLEMENTS

Substance	Function
Lutein and zeaxanthin	Antioxidant – to protect macula from oxidative damage Filter of blue light – to protect macula from light-induced damage
Vitamin C	Antioxidant – to protect macula and lens from oxidative damage
Vitamin E	Antioxidant – to protect macula and lens from oxidative damage
Zinc	Antioxidant – to protect macula and lens from oxidative damage
Selenium	Antioxidant – to improve the efficacy of other antioxidants
Copper	To prevent potential copper deficiency caused by high dose zinc supplementation
Omega-3 fatty acids	For good eye health and retinal function

the original AREDS formula.[13] The comparison was 40 mg versus 95 mg of zinc. The results indicated that there was no safety benefit in reducing the dose of zinc and that the low dose may be less effective. The recommendation was to continue with the high dose formulation.

What about lutein and zeaxanthin supplements? Level 2 evidence

One of the aims of AREDS 2 was to see if adding lutein and zeaxanthin (LZ) to the AREDS formula improved the outcome. The primary analyses demonstrated no beneficial or harmful effect.[13] Exploratory subgroup analyses showed a marked protective effect in the lowest decile of intake.

In practical terms, increasing the intake of LZ by either diet or supplements makes little difference to the progress of AMD above the equivalent of eating three-quarters of a cup of cooked spinach per week (equivalent to 15 mg of lutein). For people eating the equivalent of less than half a cup of cooked spinach per week, the benefit of LZ supplementation is massive, with a 45% reduction in the progression to late AMD (hazard ratio, 0.65; 95% CI, 0.47-0.90; p=0.01).[13] To err on the safe side, patients consuming less than 20 mg of lutein and zeaxanthin per week should take a LZ supplement.

Why no beta-carotene? Level 2 evidence

Beta-carotene was removed from the formula in AREDS halfway through the trial in subjects who were recent or current smokers because of the report of it causing lung cancer in the Alpha-Tocopherol, Beta-Carotene and Cancer Prevention Study.[14]

In the Blue Mountains Eye Study, beta-carotene intake from diet alone predicted neovascular AMD (relative risk comparing tertile 3 with tertile 1, 2.40; 95% CI, 0.98-5.91; p=0.027, for trend).[15]

Supplements containing beta-carotene should therefore be avoided and the amount in the diet minimised.

What about fish oil? Level 2 evidence

Prospective epidemiological studies have provided strong and consistent evidence that eating fish two to three times a week reduces the incidence of AMD and slows its rate of progression by about 30 to 50%.[16-19] There is consistent evidence that too much linoleic acid (which is abundant in the seed vegetable oils used in margarine, sauces and processed baked food) in the diet blocks the beneficial effect of fish. In one study in which the predominate fish meal was tuna salad with linoleic acid-rich mayonnaise, eating fish was paradoxically associated with a greater risk of AMD.[20]

There has only been one prospective clinical trial of fish oil supplementation and this showed the fish oil supplement was only effective in those patients in whom supplementation raised red cell membrane omega-3 levels.[21] The patients with highest versus the lowest tertile of red cell membrane omega-3 levels had a 68% risk reduction of the development of neovascular AMD (p=0.047). The level of red cell membrane omega-3 reflects the linoleic acid content of the diet. Results of this trial appear to suggest that, similar to the studies mentioned above on eating fish, a high linoleic acid content blocks the beneficial effect of the supplement.

Unfortunately the only other prospective trial to look at omega-3 supplementation used fatty acid ester, not fish oil, and did not monitor red cell membrane omega-3 levels.[13] It showed no benefit.

A strong recommendation should not be made on the basis of one trial. It is reasonable to advise patients that if they will not eat fish then taking a supplement may be beneficial if they reduce the linoleic acid content of their diet (i.e. avoid foods containing seed vegetable oils).

Why a tablet and not a capsule? Level 3-1 evidence

The decision in AREDS 2 to leave on the tablet formulation the patients who did not want to be randomised to low dose zinc or to no beta-carotene (n=1148) and to put

3. HOW DIETARY SUPPLEMENTS FIT IN WITH OUR ANTIOXIDANT DEFENCE SYSTEM

The retina, with its high oxygen content, unsaturated lipid rich membranes in the receptor discs and constant exposure to light, is particularly susceptible to oxidative damage. This damage is thought to play a pivotal role in the cause of AMD.[1] All the supplements mentioned in this article work as antioxidants preventing this damage.

The body's antioxidant defence system is made up of many components that function as a total symbiotic unit.[2-4] Put simply, it is a system for trapping free electrons before they can oxidise and damage tissues. In the cytoplasm, water-soluble antioxidants such as vitamin C, and in the lipid-rich membranes, fat-soluble antioxidants such as vitamin E and lutein mop up the electrons. Reduced glutathione collects the electrons from oxidised vitamin C or E, converting them back to their reduced state. The oxidised glutathione is reduced by selenium-dependent glutathione peroxidase in the mitochondria, and the electrons are then transferred to the ubiquinone system and used to power the proton pumps of the mitochondrial electron transport chain, ultimately being used in the production of ATP. Selenium, therefore, is essential to the efficient functioning of all the antioxidant components. As Australian soils are low in selenium and the Australian population is therefore relatively selenium-deficient, unlike the situation in the USA where the AREDS trial was performed, selenium is added to dietary supplements here.

Zinc is an important part of the body's antioxidant defence mechanism, in particular the inhibition of the production of reactive oxygen by transition metals.[5] Zinc levels have been shown to be low in the retina of patients with AMD, and to be associated with oxidative stress.[6,7] Although by convention we describe the AREDS formula as 'zinc plus antioxidants', it would be more accurate to describe it as an antioxidant formula. Copper is a pro-oxidant and is put in the formula because zinc alone would block copper absorption and cause a deficiency.

Lutein and zeaxanthin are carotenoids that form the pigment spot in the macula. They are derived solely from the diet and are not synthesised in the body. The macula selectively concentrates lutein and zeaxanthin to levels up to 1000 times greater than those found in any other body tissues. Lutein and zeaxanthin play dual roles as antioxidants and as an internal pair of sunglasses by being concentrated in the retina above the receptors and selectively absorbing the shorter wavelength, high-energy light, thereby protecting the receptors from unnecessary photo-oxidative damage.

The mitochondria have been shown to be abnormal in people with AMD.[8] A trial of mitochondrial nutrients including fish oil and coenzyme Q10 has shown a significant reduction in the progress of drusen.[9] Low levels of vitamin B_{12}, a key component of the mitochondrial metabolism, have been associated with a higher risk of incident AMD.

the others on a soft capsule formulation provided the first prospective pseudo-randomised study of the risks associated with putting the AREDS formula in an oil-based capsule versus a tablet.[13] The biochemical reason for not putting a highly reactive metal like copper in a capsule with a linoleic acid-rich oil is that it is likely that toxic products will be produced.[22]

The soybean oil-filled capsules as opposed to tablets have been shown to be associated with a significantly increased risk of combined cardiac and nervous system disorders (18% and 13.8%, respectively; p=0.006) and a 30% increase in neoplasia.[13]

Capsules containing copper should be assumed to be unsafe until proven otherwise. Copper-containing formulae should be prescribed only in tablet form, and preferably copper should not be combined with organic chemicals.

Why check vitamin B_{12} and vitamin D levels?

Low levels of vitamin B_{12} or vitamin D are associated with increased incident AMD.[23,24] In the Blue Mountains Eye Study, the 10-year incidence of AMD showed that a serum vitamin B_{12} deficiency of below 185 pmol/L was associated with a 2.5 higher risk of developing incident AMD.[25] A prospective randomised study showed a highly significant 40% reduction in incident AMD in patients taking vitamins B_{12} and B_6 and folic acid over seven years.[26] As epidemiological evidence showed no benefit of having a high folate or vitamin B_6 level, it is likely the vitamin B_{12} was the main driver of this effect.

In a patient with AMD or a family history of AMD, the treating doctor should be alert to a possible deficiency of vitamin B_{12} or D.

Why consider coenzyme Q10 supplementation?

A prospective masked trial of mitochondrial nutrients that included coenzyme Q10 in patients who had soft drusen showed a statistically beneficial effect on the progression of the drusen over one year.[9]

As statins reduce coenzyme Q10 levels, coenzyme Q10 supplementation should be considered in patients who are taking a statin to reduce the possible adverse effect of low levels of this coenzyme on the progression of AMD.

In patients who are taking a statin because of the presence of significant cardiovascular disease, supplementation with coenzyme Q10 200 mg and selenium 100 µg per day should be considered. As well as slowing the progress of the patient's AMD, this may also reduce their risk of cardiac death by 50%.[27]

TABLE 3. SUGGESTED USE OF DIETARY SUPPLEMENTATION IN MACULAR DEGENERATION

Dietary intake	Dietary supplement
Three or more fish meals per week and dietary lutein and zeaxanthin equivalent to one or more cups of cooked spinach per week (i.e. 20 mg of lutein/zeaxanthin)	Nil
Three fish meals per week and dietary lutein zeaxanthin equivalent to less than one cup of cooked spinach per week	Lutein 10 mg plus zeaxanthin 2 mg (several products available)
No fish irrespective of dietary intake of lutein	Lutein 10 mg, zeaxanthin 2 mg, fish oil concentrate with EPA 650 mg and DHA 350 mg, and selenium 100 µg (i.e. two tablets of Lutein-Vision Advanced)*
One to two fish meals per week irrespective of dietary intake of lutein zeaxanthin	Lutein 5 mg, zeaxanthin 1 mg, fish oil concentrate with EPA 325 mg and DHA 175 mg, and selenium 50 µg (i.e. one tablet of Lutein-Vision Advanced)*

ABBREVIATIONS: DHA = docohexaenoic acid; EPA = eicosapentaenoic acid.
* Oxidation products in fish oil are a major concern and the combination of lutein, zeaxanthin and fish oil in an opaque capsule in Lutein-Vision Advanced is optimal.

DIETARY SUPPLEMENTATION

As mentioned earlier, if dietary intake of nutrients for eye health is inadequate, nutritional supplementation may be appropriate. Such supplementation is appropriate for both people at risk of macular degeneration and those already diagnosed with it. Depending on diet, supplements may be indicated as outlined in Table 3.

Supplements that include copper and fish oil and/or LZ in the one tablet or capsule are not recommended because of the potential for toxicity.

WHAT ABOUT PATIENTS WITHOUT SIGNS OR FAMILY HISTORY OF AMD?

It is often said that the AREDS study showed that the AREDS formula had no effect on people without AMD. A lack of evidence, however, is not evidence of a lack of effect. The group without AMD was too small and followed for too short a duration for enough of them to develop AMD to detect an effect.

If the AREDS formula slows the progress of AMD in patients with significant disease, it is more likely than not to slow the progress in those who have not yet developed signs. The problem is that if a patient has no signs of AMD and no family history of the disease then the likelihood of AMD developing is small and the cost and inconvenience of taking the medications over a period of decades is considerable and so may not be justified. For someone with a family history of AMD, it is different.

A personal experience – PB

My parents had soft drusen and my paternal uncle went blind from AMD at the age of 76 years and maternal aunt at age 82 years. I do not want to take the risk of developing vision loss that I may have prevented.

My risk is high and the benefit of delaying vision loss so great that the cost and inconvenience of taking the medications is acceptable. I therefore take one Macuvision tablet (vitamin C, vitamin E, zinc and copper) per day. I am very strict with my diet but often do not eat enough fish or leafy green vegetables so I take one Lutein-Vision Advanced tablet (lutein, zeaxanthin, selenium and omega-3 fatty acids) per day. I checked my vitamin D and B_{12} levels, and as the B_{12} level was low I take a B_{12} supplement. I take coenzyme Q10 150 mg per day. I am neurotic about my weight and do as much exercise as time allows. The one intermediate sized drusen in my right eye has not changed over the past eight years.

RESOURCES FOR PATIENTS

Factsheets for patients available from the Macular Disease Foundation Australia include one titled *Nutrition and Supplements for Macular Degeneration*, available at: http://www.mdfoundation.com.au/resources/1/factsheets/NandS_Feb_2014_web.pdf.

CONCLUSION

All patients with early signs of AMD should receive general dietary and lifestyle advice and take a nutritional supplement of high dose zinc and the antioxidants vitamins C and E, based on the AREDS formula. If dietary intake of nutrients for eye health is inadequate, further supplementation with lutein, zeaxanthin, concentrated fish oil and selenium may be appropriate. MT

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A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

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