

Synopsis

This brief article aims to provide an overview of the role of nutritional supplementation for age-related macular disease, and covers the background theory, randomised controlled trials, and safety. The proposed importance of lutein is explained, and guidance given for optometrists who wish to discuss nutritional supplementation and dietary modification with their patients.

1. Age-related macular degeneration pathogenesis

There are estimated to be nearly one million visually impaired people in Britain, 90% of whom are over 65 years of age [1]. Age-related macular degeneration (AMD) is the most frequently occurring disease that results in permanent vision loss in this age group [2, 3]. Information about risk factors for AMD is limited and there are no treatment options for most of those with this condition.



Age-related macular degeneration is a condition that affects the retinal pigment epithelium (RPE), photoreceptors and choriocapillaris. Early stages of age-related macular disease (ARMD) can be described as age-related maculopathy (ARM) and later stages (including geographic atrophy and choroidal neovascularisation) can be referred to as age-related macular degeneration (AMD), in alignment with the International

Classification and Grading System [4]. Age-related macular degeneration is associated with a gradual loss of the ability of the outer retina to remove the metabolic waste products that result from normal shedding of photoreceptors. Drusen, visualised on the retina as yellow spots, are deposits of cellular debris and waste products, which accumulate between the RPE and Bruch's membrane. They are composed of mucopolysaccharides and lipids [5].

2. Antioxidant theory

It is generally thought that oxidative damage is responsible for aging and that this process has an important role in the pathogenesis of age-related conditions such as ARMD [6]. Oxidation involves the removal of electrons, and is mediated by reactive oxygen species (ROS). Reactive oxygen species is an umbrella term and includes some types of free radicals, singlet oxygen, and hydrogen peroxide. Free radicals have an unpaired electron in their outer orbit, which makes them unstable and harmful to cells in the body. In order to achieve stability they pluck electrons from other molecules, producing further ROS and fuelling disease-generating cytotoxic chain reactions [7].



Bausch & Lomb Academy of Vision Care™

The eye is particularly prone to ROS damage. The transparency of the cornea, aqueous humour, lens and retina allow continuous exposure to sunlight, which along with aging, inflammation, air pollutants, and cigarette smoke, has been shown to increase production of ROS [8, 9]. Polyunsaturated fatty acids are abundant in the retina,



predominantly found in photoreceptor outer membranes, and are readily oxidised [8, 10, 11]. Phagocytosis, a process that produces ROS, occurs within the RPE.

3. Randomised controlled trials

When investigating the effect of a particular intervention on a disease process, the gold standard type of study is the randomised controlled trial (RCT). Features of RCTs used in studying the effects of nutritional supplementation on ARMD should include:

- Random assignment of participants to treatment and control groups
- 'Double masking' – external coding of treatment and placebo tablets
- Treatment and placebo tablets identical in appearance and taste
- Code broken at end of trial and the differences between groups analysed

4. The Age-Related Eye Disease Study (AREDS)

The AREDS Study investigated the effect of high dose supplementation with the following nutrients:

Vitamin C (ascorbic acid)	113mg	
Vitamin E (dl-alpha tocopheryl acetate)	68mg	(100IU)
Vitamin A (beta-carotene)	4871mg	(7160IU)
Zinc (zinc oxide)	17.4mg	
Copper (cupric oxide)	0.4mg	

More than 3500 participants were grouped into four main categories according to ARM or AMD stage (see table 1). Participants in categories 2, 3 and 4 were randomised into four arms; 1) antioxidants, 2) zinc, 3) antioxidants plus zinc, 4) placebo.



www.academyofvisioncare.com

Bausch & Lomb Academy of Vision Care™

Category 1	Range from completely normal macula to a few small drusen
Category 2	Multiple small drusen, single or non-extensive intermediate-sized drusen, pigment abnormalities
Category 3	Absence of advanced AMD in both eyes, with at least one large drusen at macular centre, or extensive intermediate drusen or geographic atrophy not involving the central macula
Category 4	No advanced AMD in one eye, with visual impairment caused by AMD in the fellow eye

Table 1: AREDS categories [12]

There was a 25% reduced risk of disease progression in category three and four participants taking zinc plus antioxidants, as well as a 'suggestive' reduction in risk for the zinc arm [13].

5. Safety and supplementation



Eye-care practitioners require information about the benefits, and potential hazards, of ocular nutritional supplements in order to be able to discuss their use with patients. It should be emphasised that the risk of side effects from nutrients is much lower than from over the counter or prescription drugs. As an example, the National Health and Nutrition Examination Survey II estimated that 35 % of the US population use vitamin A supplements [14], and the rate of toxic reactions has been reported as 1 case per 1.1 million per year exposed.

A comprehensive review of the contraindications and adverse reactions relating to nutritional supplementation can be found in Ophthalmic and Physiological Optics [15]. With regard to the AREDS formulation, the most important potential side effects to be aware of are:

- Doses of 20 mg/day beta-carotene have been associated with an increased risk of lung cancer in smokers [16, 17].
- Concurrent vitamin E and warfarin use has been associated with abnormal bleeding [18].



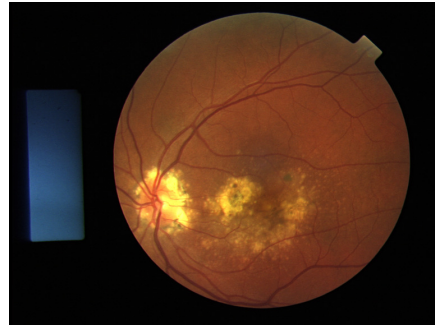
Acute zinc toxicity has been reported with doses of 200 mg or more [19]. It is important to warn patients about potential side effects if they take more than one supplement that contains zinc.



www.academyofvisioncare.com

6. Lutein, zeaxanthin, meso-zeaxanthin and the macular pigment

Since the AREDS started, interest has been raised into the protective role of the oxygenated xanthophylls group of carotenoids in the eye, particularly the retina. Lutein and its isomers are the only carotenoids present in the lens [20] and retina [21-24] and are also known as macular pigment (MP). The proposed specific function of xanthophylls at the macula [22] is supported by the fact that macular levels are several thousand times higher than serum levels [25]. This may be explained by the discovery of a putative lutein-binding protein in the retinae of human eyes [26], which binds with high affinity and specificity to lutein and other xanthophylls.



The MP may reduce photo-oxidative damage to the retina and therefore protect against age-related deterioration [27]. The absorbance spectrum of MP peaks at 460 nm and it is purported to act as a broadband filter, reducing the sensitivity of the macular region to short wavelength light which is most damaging in the 440 to 460 nm range [28, 29]. Zeaxanthin has been reported to be the superior photo-protector during prolonged UV exposure. The shorter time-scale of protective efficacy of lutein has been attributed to oxidative damage of the carotenoid itself [30].

7. The Lutein Antioxidant Supplementation Trial (LAST) and Aston RCT

The Lutein and Antioxidant Supplement Trial (LAST) was a 12-month RCT designed to evaluate the effect of 10 mg unesterified lutein alone or 10 mg lutein combined with additional carotenoids and antioxidants/minerals on MP optical density and objective visual outcome measures in 90 subjects with atrophic AMD. Glare recovery and contrast sensitivity significantly improved with both interventions, although it is worth noting that the study population was 95.6 % male [31].

A second randomised controlled trial took place in a clinical setting within a research institute and an optometric practice in the UK. Participants diagnosed with ARM were randomised to placebo or daily supplementation with a lutein and antioxidant formulation (see table 2).

Nutrient	Dose
Lutein esters	6 mg
Retinol	750 µg
Vitamin C	250 mg
Vitamin E	34 mg
Zinc	10 mg
Copper	0.5 mg

Table 2: Intervention constituents for the UK trial



Bausch & Lomb Academy of Vision Care™

This study found no significant difference in the change contrast sensitivity, measured using the Pelli-Robson chart, between groups after nine months of supplementation [32]. The study had 80% power at the 5 % significance level to detect a change in contrast sensitivity of 0.3 log units. The results of these two trials may suggest that at least 10 mg per day of supplemental lutein is required to produce any positive effect.

8. Bioavailability

Investigators concluded that the bioavailability of lutein from eggs is higher than that from other sources, and that this may be related to the fact that within eggs, lutein is located in the digestible lipid matrix [33]. It should be noted that the eggs used in this study contained approximately five times the amount of lutein than conventional eggs. Nevertheless, the results provide useful information about the bioavailability of lutein from different sources, suggesting that a lipid base may be optimum for supplements.

9. Government guidelines

The UK Food Standards Agency recommends that one third of the food we eat each day should consist of fruit and vegetables. We should aim to eat at least five portions per day, and these portions should be from a range of fruit and vegetables.



www.academyofvisioncare.com

Table 2 gives some examples of portion sizes.

ONE portion = 80g = any of these

1 apple, banana, pear, orange or other similar sized fruit

2 plums or similar sized fruit

½ a grapefruit or avocado

1 slice of large fruit, such as melon or pineapple

3 heaped tablespoons of vegetables (raw, cooked, frozen or tinned)

3 heaped tablespoons of beans and pulses (however much you eat, beans and pulses count as a maximum of one portion a day)

3 heaped tablespoons of fruit salad (fresh or tinned in fruit juice) or stewed fruit

1 heaped tablespoon of dried fruit (such as raisins and apricots)

1 handful of grapes, cherries or berries

a dessert bowl of salad

a glass (150ml) of fruit juice (however much you drink, fruit juice counts as a maximum of one portion a day)

Table 2: The UK Food Standards Agency guidelines on fruit and vegetable portion sizes.



Bausch & Lomb Academy of Vision Care™

Lutein can be obtained in various foods, but the best sources are green leafy vegetables such as spinach and kale (see table 3).

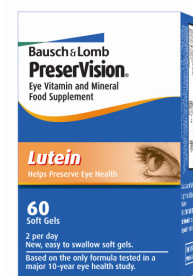
FOOD	SERVING SIZE	LUTEIN/ZEAXANTHIN (mg)
Kale, cooked	1 cup	20.5
Collard greens, cooked	1 cup	15.4
Spinach, cooked	1 cup	12.6
Turnip greens, cooked	1 cup	12.1
Broccoli, cooked	½ cup	4.0
Spinach, raw	1 cup	3.6
Aubergine, raw	1 cup	2.6
Peas, cooked	1 cup	2.2
Broccoli, raw	1 cup	2.1
Corn, cooked	½ cup	1.5
Lettuce, cos or romaine	1 cup	1.5
Brussels sprouts, cooked	½ cup	1.1
Papaya	1 papaya	0.3
Peaches	1 peach	0.2
Apple	1 apple	0.04

Table 3: Lutein and zeaxanthin content of different foods. A cup represents a standard serving size, and a portion of this size will look similar to the size of a clenched fist.

10. Patient recommendations

All patients should be encouraged not to smoke, to wear sunglasses when outdoors on bright days, and to eat at least five portions of fruit and vegetables per day, with one portion ideally consisting of a green leafy vegetable.

Patients with AREDS category 3 or 4 AMD may consider taking the AREDS formulation, such as PreserVision original (Bausch and Lomb), as long as they do not smoke. For those who do smoke, a modified AREDS formulation is also available without beta-carotene, such as PreserVision Lutein (Bausch and Lomb). Patients should be advised to discuss nutritional supplement use with their GP.



Patients with ARM, or who have a family history of ARMD may be advised specifically to increase their lutein intake. For those patients who, for whatever reason, cannot increase their intake of green leafy vegetables a supplement containing lutein can be advised. Current literature suggests that a supplement containing at least 10 mg lutein that is combined with oil should provide the best bioavailability.



www.academyofvisioncare.com

Bausch & Lomb Academy of Vision Care™

References

1. Evans, J. and R. Wormald, *Is the incidence of registerable age-related macular degeneration increasing?* British Journal of Ophthalmology, 1996. 80(1): p. 9-14.
2. Goldberg, J., et al., *Factors Associated with Age-Related Macular Degeneration - an Analysis of Data from the 1st National-Health and Nutrition Examination Survey.* American Journal of Epidemiology, 1988. 128(4): p. 700-710.
3. Elton, M.G., J, *Exudative age-related macular degeneration.* Optometry Today, 2000. October: p. 42-45.
4. Bird, A.E.C., et al., *An International Classification and Grading System for Age-Related Maculopathy and Age-Related Macular Degeneration.* Survey of Ophthalmology, 1995. 39(5): p. 367-374.
5. Newsome, D., A. Hewitt, and W. Huh, *Detection of specific extracellular matrix molecules in drusen, Bruch's membrane, and ciliary body.* American Journal of Ophthalmology, 1987. 104: p. 373-381.
6. Beatty, S., et al., *The role of oxidative stress in the pathogenesis of age-related macular degeneration.* Survey of Ophthalmology, 2000. 45(2): p. 115-134.
7. Diplock, A., *Antioxidant nutrients and disease prevention: an over view.* American Journal of Clinical Nutrition, 1991. 53: p. 189S-193S.
8. Machlin, L. and A. Bendich, *Free radical tissue damage: protective role of antioxidant nutrients.* FASEB Journal, 1987. 1: p. 441-445.
9. Borish, E., W. Prior, and S. Venuugopal, *DNA synthesis is blocked by cigarette tar-induced DNA single strand breaks.* Carcinogenesis, 1987. 8: p. 1517-1520.
10. Beardsley, T., *The A Team. Vitamin A and its cousins are potent regulators of cells.* Sci Am, 1991: p. 16-19.
11. Van der Hagen, A., et al., *Free radicals and antioxidant supplementation: a review of their roles in age related macular degeneration.* J Am Optom Assoc, 1993. 64: p. 871-878.
12. Kassoff, A., et al., *A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss - AREDS Report No. 8.* Archives of Ophthalmology, 2001. 119(10): p. 1417-1436.
13. The AREDS Research Group, *A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss - AREDS Report No. 8.* Archives of Ophthalmology, 2001. 119(10): p. 1417-1436.
14. Koplan, J., et al., *Nutrient intake and supplementation in the United States (NHANES II).* American Journal of Public Health, 1986. 76: p. 287-289.
15. Bartlett, H. and F. Eperjesi, *Adverse reactions and contraindications for ocular nutritional supplements.* Ophthalmic and Physiological Optics, 2005. 25(3): p. 179-194.
16. The ATBC Cancer Prevention Study Group, *The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers.* New England Medical Journal, 1994. 330: p. 1029-1035.
17. Leo, M.A. and C.S. Lieber, *Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial.* Journal of the National Cancer Institute, 1997. 89(22): p. 1722-1723.
18. Corrigan, J. and F. Marcus, *Coagulopathy associated with vitamin E ingestion.* JAMA, 1974. 230: p. 1300-1301.
19. Expert Group on Vitamins and Minerals, *Safe Upper Limits for Vitamins and Minerals.* 2003, Food Standards Agency.



www.academyofvisioncare.com

Bausch & Lomb Academy of Vision Care™

20. Yeum, K.-J., et al., *Measurement of Carotenoids, Retinoids, and Tocopherols in Human Lenses*. Investigative Ophthalmology and Visual Science, 1995. 36: p. 2756-2761.
21. Bone, R., J. Landrum, and S. Tarsis, *Preliminary identification of the human macular pigment*. Vision Research, 1985. 25: p. 1531-1535.
22. Handelman, G., E. Dratz, and C. Reay, *Carotenoids in the human macula and the whole retina*. Invest Ophthalmol Vis Sci, 1988. 29: p. 850-855.
23. Handeman, G., D. Snodderly, and A. Adler, *Measurement of carotenoids in human and monkey retinas*. Methods in Enzymology, 1992. 213: p. 220.
24. Bone, R., et al., *Stereochemistry of the human macular carotenoids*. Investigative Ophthalmology and Visual Science, 1993. 34: p. 2033-2040.
25. Schmitz, H., et al., *Analysis of lutein in human and animal tissues*. Methods in Enzymology, 1993. 214: p. 102-116.
26. Yemelyanov, A., N. Katz, and P. Bernstein, *Ligan-binding characterization of xanthophyll carotenoids to solubilized membrane proteins derived from human retina*. Experimental Eye Research, 2001. 72: p. 381-392.
27. Hammond, B., B. Wooten, and D. Snodderly, *Preservation of visual sensitivity of older individuals: association with macular pigment density*. Investigative Ophthalmology and Visual Science, 1998. 39: p. 397-406.
28. Pease, P., A. Adams, and E. Nuccio, *Optical density of human macular pigment*. Vision Research, 1987. 27: p. 705-710.
29. Reading, V. and R. Weale, *Macular pigment and chromatic aberration*. Journal of the Optometric Society of America, 1974. 64: p. 231-238.
30. Sujak, A., et al., *Lutein and Zeaxanthin as Protectors of Lipid Membranes against Oxidative Damage: The Structural Aspects*. Archives of Biochemistry and Biophysics, 1999. 15: p. 301-307.
31. Richer, S., et al., *Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial)*. Optometry, 2004. 75: p. 216-230.
32. Bartlett, H.E. and F. Eperjesi, *Effect of lutein and antioxidant dietary supplementation on contrast sensitivity in age-related macular disease: a randomized controlled trial*. European Journal of Clinical Nutrition, 2007. 61(9): p. 1121-1127.
33. Chung, H.-Y., H. Rasmussen, and E. Johnson, *Lutein bioavailability is higher from lutein-enriched eggs than from supplements and spinach in men*. Journal of Nutrition, 2004. 134: p. 1887-1893.



www.academyofvisioncare.com