

Clinician to Clinician

This issue's column: Zeaxanthin- The "Other" Macular Pigment

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Clinician to Clinician: A bimonthly case report or topical discussion

Zeaxanthin is a *xanthophyll* contained within the retina and crystalline lens. Xanthophylls are a sub-class of the *carotenoids*, a large group of plant pigments responsible for the colors of bright fruits and vegetables. Along with its two sister compounds meso-zeaxanthin and lutein, zeaxanthin comprises the macular pigment (see Figure 1). Zeaxanthin may serve as a filter that absorbs the blue part of the light spectrum. It has been shown to act as a potent antioxidant, quenching free radicals associated with the pathogenesis of age-related macular degeneration (AMD).¹ Zeaxanthin is found in yellow fruits and vegetables, and in dark green leafy vegetables like spinach, kale, and collard greens.

Age-related macular degeneration (AMD) is a leading cause of vision loss in Canada and the United States. AMD's adverse effects on quality of life and its economic impact on health care systems have caused a heightened interest in its prevention and early detection, as well as novel treatment approaches for both the non-exudative (dry) and exudative (wet) forms (see Figure 2 and Figure 3). Risk factors for AMD are listed in Table 1. Low levels of lutein and zeaxanthin in the diet, serum or retina may result in an increased risk of AMD. Nutritional therapy is one means of proactive intervention.

Much of the early macular pigment research, including supplementation studies, focused on lutein exclu-

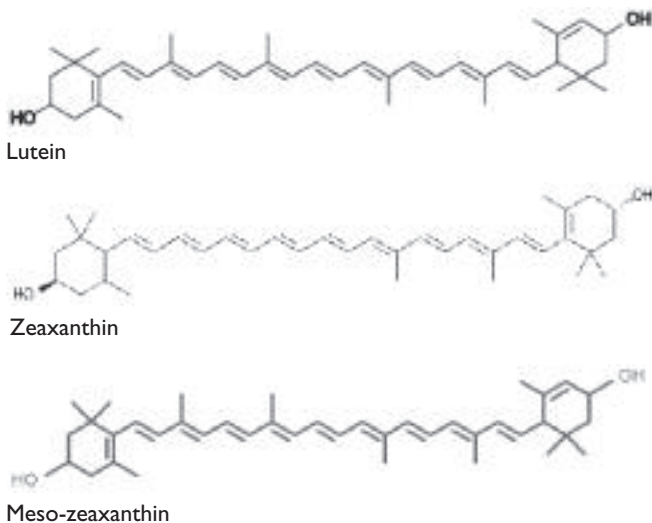


Figure 1. Chemical structures of the macular pigments



Figure 2. Low levels of lutein and zeaxanthin may result in an increased risk of AMD. This is an eye with intermediate drusen in non-exudative AMD.

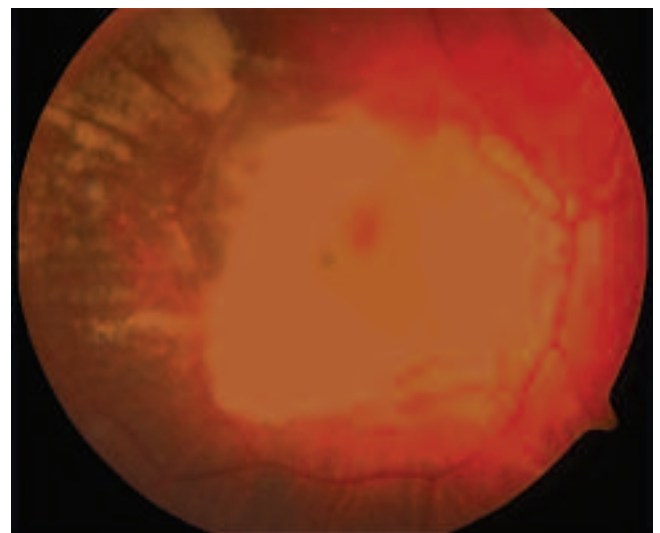


Figure 3. This is an eye with Choroidal Neovascularization in exudative AMD.

sively. We now have epidemiological evidence that suggests zeaxanthin may be of equal or even greater importance in protecting the fovea. In this brief topical review, we will summarize the importance of the macular pigments, and that of zeaxanthin in particular, for protection against the development and progression of AMD. We will also discuss the role of the optometrist in the preservation of macular health.

Table 1. Risk factors for AMD^{16,17}

Age – The most important risk factor
Gender – Women are more at risk than men
Smoking – A modifiable risk factor
Obesity – As body mass index increases so does the risk of advanced AMD
Race – More prevalent in whites
Family history (genetics)
Hypertension/Cardiovascular Disease
Dietary habits – Leafy green vegetable (carotenoids) consumption is linked with a decreased risk
Elevated C-reactive protein levels
Elevated homocysteine levels

The Importance of Macular Pigments

The macular lutein to zeaxanthin ratio is approximately 1:1. Within the central aspect of the macula, however, zeaxanthin is the predominant pigment, whereas in the peripheral aspect, lutein is more abundant. Relative to lutein, the concentration of zeaxanthin in the adult retina increases with proximity to the center of the fovea. This suggests that zeaxanthin may have a specific function in the fovea.²

Both lutein and zeaxanthin may have the ability to trap short-wavelength light, thus protecting the outer retinal layers, pigment epithelium, Bruch's membrane, and choroid from oxidative damage.³ Other personal factors related to oxidation include cardiovascular disease and low ocular melanin content. A growing body of evidence suggests that the macular pigments have a chief role in protecting against the harmful effects of oxidative stress by quenching free radicals. Sources of free radicals include cigarette smoke, radiation, certain drugs, air pollutants, and other environmental toxins.³

The POLA (Pathologies Oculaires Liées à l'Age) Study separately assessed the associations of plasma concentrations of lutein and zeaxanthin, as well as that of other carotenoids, with the risk of AMD in a Mediterranean population. After multivariate adjustment, the highest quintile of plasma zeaxanthin was most significantly associated with reduced risk for AMD. Risk for AMD was also inversely associated with combined plasma lutein and zeaxanthin, and tended to be associated with plasma lutein, to a lesser extent. These results are consistent with previous epidemiological studies and are suggestive of a protective role of the xanthophylls, and in particular zeaxanthin.⁴

One of the first large studies on carotenoids was the Eye Disease Case Control Study, in which various dietary components were correlated to the relative risk for developing AMD. Results showed a significantly lower risk for developing AMD in people with high amounts of lutein + zeaxanthin in their blood. Also, people

whose diet contained the most lutein + zeaxanthin had a significantly lower risk for AMD than those whose diet contained the least amount. Dietary studies have also confirmed the association between frequent consumption of spinach or collard greens, particularly good sources of lutein and zeaxanthin, and lower AMD risk.⁵

Similar results were found in a recent analysis of a national dietary study, the Third National Health and Nutrition Examination Survey or NHANES III. This analysis showed that consuming 6 mg per day of lutein + zeaxanthin was associated with a reduced risk for developing AMD.⁶

The amount of macular pigment in the retina can now be quantified in a clinical setting. The most studied method for macular pigment quantification is a psychophysical technique called Heterochromatic Flicker Photometry (HFP). HFP uses flickering blue and green light targets to yield a measurement reported in density units as Macular Pigment Optical Density (MPOD). HFP does not require pupil dilation but does require some attention and training in order to yield reliable results. Lower MPOD can be associated with increased risk for AMD. In addition, several studies have shown that lower MPOD can be associated with several other risk factors for AMD.⁷

How much is enough?

Given that the body cannot produce the retinal carotenoids on its own, it seems prudent for people to obtain appropriate amounts of these nutrients from their daily diet. Eating five servings of fruits and vegetables each day can provide about 5 to 6 mg of carotenoids, including lutein and zeaxanthin. However, the majority of people do not eat five daily portions of fruits and vegetables. Fortunately, vitamins, minerals and ocular supplements containing lutein and zeaxanthin are available.

The US National Institutes of Health (NIH) has begun a nationwide study to see if a modified combination of vitamins, minerals, and fish oil can further slow the progression of vision loss from AMD. This new study, called the Age-Related Eye Disease Study 2 (AREDS 2), will build upon results from the earlier Age-Related Eye Disease Study (AREDS 1). The original study found that antioxidant vitamins and minerals (vitamins C and E, beta-carotene, zinc), taken by mouth, reduced the risk of progression to advanced AMD by 25 percent in patients with intermediate AMD or advanced AMD in one eye, but not the other.⁸ It is important to note that in AREDS 1, supplementation did not show a benefit for patients with early stage disease.

At the conception of the AREDS 1 trial, zeaxanthin and lutein were not commercially available. AREDS 2 will refine the protocol of the original study by adding lutein and zeaxanthin and the omega-3 fatty acids DHA and EPA (derived from fish and vegetable oils) to the formulation. The main study objective is to determine if

these nutrients will decrease a person's risk of progression to advanced AMD.⁹

There are currently no Dietary Reference Intake (DRI) standards for lutein or zeaxanthin in the US or Canada. No adverse effects of human supplementation with lutein or zeaxanthin have been reported, so they are considered relatively safe.^{1,10,11} Previous safety and efficacy studies used daily dosages of up to 30mg of zeaxanthin and 40mg of lutein. The macular pigment dosage being studied in AREDS 2 is lutein at 10 mg/day plus zeaxanthin at 2 mg/day.⁹

Several studies found a significant increase in MPOD after supplementation.¹⁰ More recently, there is some evidence that higher levels of lutein and zeaxanthin in serum and the retina may be associated with improved visual function.¹²

A Pro-active Strategy

The optometrist can be an important resource for patients seeking to achieve optimum macular health and protection. We start by advising patients to eat a balanced diet that is high in fish, and whole grains, emphasizing fruits, vegetables (especially greens), and fat-free or low-fat dairy products. The diet should also include lean meats, poultry, beans, eggs, and nuts. It should be low in saturated fats, trans fats, cholesterol, salt (sodium), and added sugars.¹³ A broad-spectrum multivitamin may be advisable for patients who are unable to achieve these dietary goals. Some multivitamin products may contain varying amounts of lutein and zeaxanthin, in addition to other vitamins and minerals that are important in ocular health (such as vitamins C, E, and zinc).

For patients with early signs, or those at risk for AMD due to genetic, personal, systemic, or environmental factors, we supplement with both zeaxanthin and lutein. First, we obtain a baseline MPOD measurement with HPF. For zeaxanthin, a dosage of approximately 4-mg to 10-mg per day, depending upon the patient's diet (especially green vegetable intake), body mass, MPOD, and other health factors, is generally appropriate. For lutein, a dosage of approximately 6-mg to 20-mg per day is generally appropriate, again depending upon the various patient characteristics. We usually supplement for 6 months before rechecking the MPOD.

Most commercially available lutein/zeaxanthin combination supplements contain significantly more lutein than zeaxanthin. However, new products are now available with amounts of zeaxanthin up to 10mg in a soft gel or capsule. Lutein supplements are typically available in either 6-mg or 20-mg tablets or capsules. While the 6-mg dose was based on early studies, the 20-mg dose has become more common and is usually taken once daily.

If a patient meets the AREDS 1 criteria (intermediate AMD or advanced AMD in one eye but not the other), we usually supplement with the AREDS 1 formulation. In addition, we may also recommend zeaxanthin and

lutein supplementation (on a case-by-case basis) for patients in this group, depending on their MPOD and whether they include greens in their diet.

In recommending vitamins and supplements, it is important to note some important caveats. In both the Beta-Carotene and Retinol Efficacy Trial (CARET) and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (ATBC), a relationship was found between beta-carotene intake and an increased risk for lung cancer in males who smoke.^{14,15} If you have questions about a vitamin supplement's appropriateness for a particular patient, it would be prudent to first contact the patient's primary physician, pharmacist, or a nutritionist before proceeding.

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