Carotenoids for Ocular Health

An expert review of the scientific evidence and best nutritional practices

Highlights from a roundtable discussion held March 24, 2014 in New York, New York

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Introduction

As primary eye care providers, optometrists have the opportunity and responsibility to play a valuable role in counseling patients about strategies for preserving eye health. The importance of providing this education is highlighted by data that describe a high and rising prevalence of age-related eye diseases. An estimated 1.8 million Americans have vision loss associated with advanced age-related macular degeneration (AMD), while another 7.3 million are at substantial risk; in addition, 20.5 million Americans aged 40 years and older are affected by cataract. The number of individuals with these conditions is expected to increase dramatically in the near future as the result of increasing life expectancy and growth of the aging population.[1]

Nutritional modification is one way to reduce the risk and associated burdens of AMD and cataract, and use of supplements containing lutein and zeaxanthin, dietary carotenoids that are components of macular pigment, is a proven strategy. Using data from published clinical outcomes studies, a 2013 cost analysis determined that daily consumption of supplements containing lutein, 10 mg, and zeaxanthin, 2 mg, by all adults aged 55 years and older with cataract or AMD would result in a 23% relative risk reduction in AMD, a 15% relative risk reduction in cataract, and potentially more than $7 billion in cumulative net health care cost savings by the year 2020.[2]

Some ocular supplements also contain the nondietary carotenoid meso-zeaxanthin, a third component of macular pigment that is commercially obtained by synthesis from lutein. However, a careful review of available information provides reason to question the need for meso-zeaxanthin supplementation and also raises concern about its use.

Recently, a panel of leading researchers and experts on nutrition and ocular health was convened to discuss the scientific evidence pertaining to the use of lutein, zeaxanthin, and meso-zeaxanthin and their clinical relevance. Highlights of that meeting are captured in this monograph. We hope optometrists will find the information educational and useful as they aim to help their patients maintain good vision throughout their lifetimes.

The Role of Lutein and Zeaxanthin in Reducing Risk and Attenuating Eye Disease

Dr Richer: Lutein and zeaxanthin are dietary nutrients found in the eye as components of the macular pigment and within the crystalline lens. Lutein and zeaxanthin are antioxidants that protect against light-induced oxidative stress, and they also act as filters, absorbing harmful blue light.

> **Lutein and zeaxanthin act as "internal sunglasses", providing protection against damaging light.** —Dr Richer

The presence of lutein and zeaxanthin in macular pigment was first described in 1985.[3] In 1994, results from the Dietary Ancillary Study of the Eye Disease Case-Control Study associated higher dietary intake of carotenoids with a decreased risk for catastrophic advanced AMD and showed that the strongest association was with lutein and zeaxanthin.[4] Since then, numerous studies have been published reporting benefits of lutein and zeaxanthin for protecting against age-related eye diseases and improving visual function. The results of the Age-Related Eye Disease Study 2 (AREDS2) established supplementation with lutein and zeaxanthin as beneficial for patients at risk for progression to advanced AMD who have low dietary lutein and zeaxanthin intakes, and also showed it had benefits for reducing cataract-related risks.[5-7]

Results from the initial AREDS—which showed that higher dietary lutein/zeaxanthin consumption was associated with a reduced risk for having large or extensive intermediate drusen, geographic atrophy, and neovascular AMD[8]—combined with other observational data associating increased intake of these carotenoids with lower AMD risk provided the rationale for AREDS2 to investigate whether lutein/zeaxanthin supplementation could reduce progression to advanced AMD in individuals at risk.[5] In the primary analysis, adding lutein 10 mg/zeaxanthin 2 mg to the original AREDS formulation did not significantly reduce the risk for progression to advanced AMD.[5] Additional preplanned analyses, however, identified several statistically significant benefits of lutein/zeaxanthin supplementation.[5-7] A main effects analysis showed that compared with no lutein/zeaxanthin, treatment with these 2 nutrients reduced the risk for AMD progression by 10% (*P*=.04), and a secondary analysis found that supplementation with lutein/zeaxanthin reduced the risk for AMD progression by 26% (*P*=.01) for study participants who were in the lowest quintile of dietary lutein/zeaxanthin intake at baseline [**Figure 1**].[5]

Figure 1. For participants in the lowest quintile of dietary intake of lutein/zeaxanthin (L/Z) in AREDS2, supplementation with L/Z vs no L/Z significantly reduced the risk of progression to advanced AMD by 26%.[5]

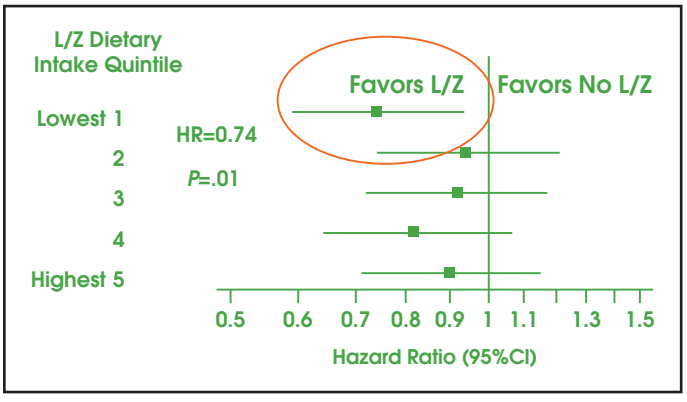
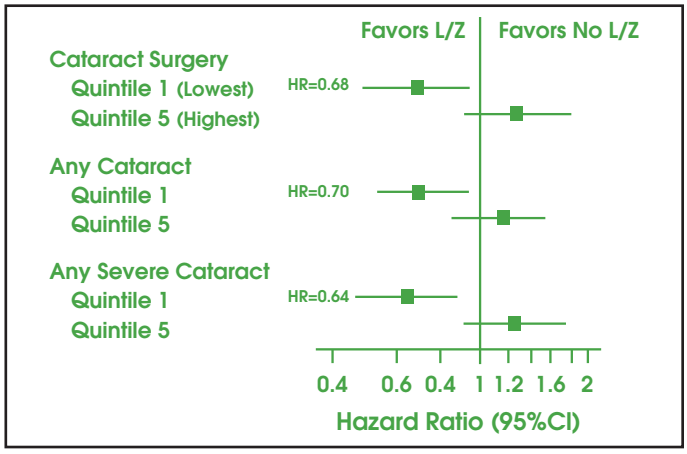


Figure 2. Cataract outcomes from AREDS2 with patients stratified by baseline dietary intake of lutein/zeaxanthin (L/Z). For participants in the lowest quintile of dietary intake of L/Z, supplementation with L/Z significantly reduced risks for progression to cataract surgery, any cataract, and any severe cataract.[7]

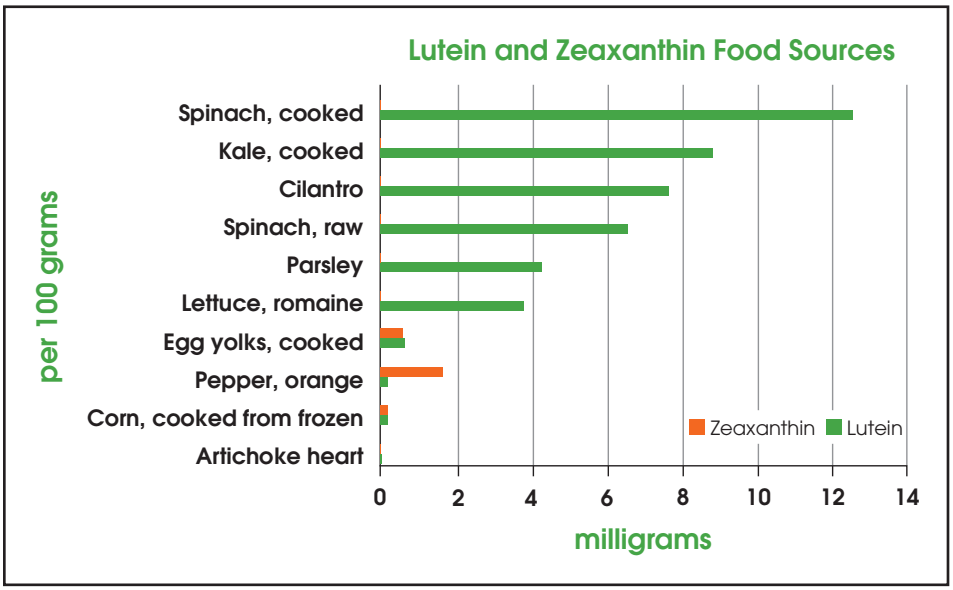


Furthermore, the risk for developing advanced AMD was reduced by 18% among subjects who received a supplement with lutein/zeaxanthin and no beta-carotene compared with subjects treated with beta-carotene and no lutein/zeaxanthin.[6]

Analyses of cataract outcomes in AREDS2 also showed benefits of lutein/zeaxanthin supplementation among persons in the lowest quintile of dietary lutein/zeaxanthin intake, including significant reductions in progression to cataract surgery (32%), cataract development (30%), and severe cataract development (36%) [**Figure 2**].[7]

Based on the efficacy data and the finding that beta-carotene was associated with an increased rate of lung cancer, the AREDS2 investigators suggested that substituting lutein and zeaxanthin for beta-carotene in the AREDS formulation could provide a safer, more efficacious supplement.[6]

Figure 3. Lutein/zeaxanthin in common sources (mg/100 g).[12]



Lutein and Zeaxanthin in the Diet

Dr Richer: There are more than 600 carotenoids in nature, of which 50 are found in the food chain, and approximately 12 are measured in the human bloodstream, but lutein and zeaxanthin are the only 2 naturally occurring carotenoids found in the macula.[9-11] Although lutein and zeaxanthin are found in a variety of foods, available data indicate the foods containing these nutrients are not abundantly consumed by the average American.

What are the best dietary sources for lutein and zeaxanthin, and what do we know about typical intake levels?

Dr Johnson: Relatively few foods account for approximately 90% of lutein and zeaxanthin intake in the American diet.[12,13] The main sources for lutein are green leafy vegetables, such as spinach and kale, and certain herbs, especially cilantro, parsley, and oregano; the best sources for zeaxanthin are orange peppers, corn, and corn products [**Figure 3**].

When estimating average daily dietary intake, we found that most people, regardless of sex or ethnicity, obtain less than 1.2 mg of lutein and less than 0.12 mg of zeaxanthin.[13] Those levels are far below the quantities that have been shown to be beneficial for reducing risk for AMD and its progression. For example, when participants in the Dietary Ancillary Study were divided into quintiles by dietary lutein/zeaxanthin intake, only those in the highest quintile, whose median lutein/zeaxanthin intake was 5.8 mg/d, had a statistically significant reduction in AMD risk compared with those in the quintile with the lowest intake.[4] In AREDS2, lutein was supplemented at a dose of 10 mg/d and zeaxanthin at 2 mg/d.

Dr Richer: The AREDS2 participants were also considered to be well-nourished and had significantly higher lutein/zeaxanthin serum levels at entry compared with the general population.[5] Even so, supplementation with lutein and zeaxanthin significantly reduced the risk for progression to advanced AMD in this well-nourished population.

What do you see as the take-home points from these data?

Dr Hitchmoth: I think the data reinforce that most patients are not getting enough lutein and zeaxanthin through their diet and underscore the need for eye care providers to be talking to patients about nutrition and the benefits of lutein and zeaxanthin.

Dr Pizzimenti: If we consider that the typical American adult consumes less than 2 mg of lutein and zeaxanthin, combined, daily, the good news from AREDS2 is that the subjects in the lowest quintile of lutein and zeaxanthin consumption benefited the most from supplementation with those carotenoids in terms of reduced risks for AMD progression and cataract.

Dr Ferrucci: The AREDS2 patients in the lowest quintile of lutein/zeaxanthin intake had a median daily lutein/zeaxanthin intake at study entry of approximately 0.7 mg.[5] It is my belief that most patients we see in our clinics and offices are probably more like the lowest-quintile AREDS2 patients in terms of their daily lutein/zeaxanthin intake.

I also think that while it is possible to increase lutein and zeaxanthin intake by dietary modification, it is unlikely that most patients will begin eating sufficient quantities of the healthy foods that are rich in these nutrients. Supplementation with lutein and zeaxanthin is important to fill in their dietary gap.

Dr Richer: Determining dietary intake of lutein and zeaxanthin can be time-consuming and unreliable. Measurement of macular pigment optical density (MPOD) offers an easy, noninvasive, point-of-care test to evaluate patients for dietary intakes of lutein and zeaxanthin and to identify those who may obtain the greatest benefit from supplementation.

Data from studies in US populations show MPOD is <0.2 du in approximately 43% of adults tested.[14] At that low MPOD level, approximately half of harmful blue light will reach the photoreceptors.[15]

There are commercially available devices for determining MPOD. In addition to its value for identifying patients likely to have a low intake of lutein and zeaxanthin, because MPOD represents a tangible numerical measurement, it provides a benchmark for clinicians to evaluate compliance in patients who start supplementation and also can motivate patients to use ocular vitamins.

Meso-Zeaxanthin: Facts, Fiction, and Safety Issues

Meso-zeaxanthin Facts

Dr Richer: Some ocular health products sold in the marketplace today contain meso-zeaxanthin in addition to lutein and zeaxanthin. Although meso-zeaxanthin is the third component of macular pigment and is similar to lutein and zeaxanthin in structure—in fact, meso-zeaxanthin is a stereoisomer of zeaxanthin—it differs from zeaxanthin and lutein in several important ways [**Table 1**]. It is important for eye care providers to understand this information when they are counseling patients on use of supplements for ocular health.

Although theoretically meso-zeaxanthin may be present as an impurity in lutein and zeaxanthin supplements as the result of the manufacturing process for lutein and zeaxanthin, its actual presence is unknown and would not exceed more than trace levels.

Whereas lutein and zeaxanthin are found naturally in the diet and deposited in the macula through preferential uptake in the eye, meso-zeaxanthin is not present in any conventional dietary source. Instead, the presence of meso-zeaxanthin in macular pigment is the result of the body's enzymatic conversion of dietary lutein.

Dr Johnson, you have conducted research both on the conversion of lutein to meso-zeaxanthin in the body as well as on trying to identify meso-zeaxanthin in food sources. Please tell us about those studies.

Dr Johnson: We performed a study in a primate model fed a xanthophyll-free diet and found that meso-zeaxanthin was present in the retina after animals received supplementation with lutein, but not when their diet was supplemented with zeaxanthin.[16] This study proved that meso-zeaxanthin in macular pigment arises from in vivo conversion of lutein and not of zeaxanthin.

We also undertook a study to identify whether meso-zeaxanthin was present in a variety of fish and seafood.[17] We focused on these food sources because, to our knowledge, the only researchers who previously reported on the natural isolation of

Table 1. Facts: Meso-zeaxanthin vs Lutein and Zeaxanthin

Structure	Meso-zeaxanthin is a stereoisomer of zeaxanthin. Meso-zeaxanthin, lutein, and zeaxanthin are similar in their structures.
Food sources	Meso-zeaxanthin is not found in foods that are typically consumed and is commercially produced from lutein by a wholly synthetic chemical process.[17-19] Lutein and zeaxanthin are found in many typically consumed foods.[12] [**see Figure 3**]
Anatomic distribution	Meso-zeaxanthin is present only in the macula and created through a conversion from lutein.[16,17,26] Lutein and zeaxanthin are found in the macula, brain, skin, breast, and adipose tissue.[20-23]
Published evidence base (research pertaining to eye health)*	Meso-zeaxanthin—first human paper published 2007;[35] total of 8 reported human clinical trials including only 263 subjects treated for no more than 24 months; no study evaluated meso-zeaxanthin without concomitant lutein and/or zeaxanthin Lutein/zeaxanthin—first human paper published 1995;[34] total of 130+ clinical trials including >20,000 subjects
Safety data (pertaining to supplementation)	Meso-zeaxanthin—the safety of long-term meso-zeaxanthin supplementation is unknown Lutein/zeaxanthin—there is a 20-year history of supplementation including a 4000+ subject, 5-year study (AREDS2)[5]

*Data based on PubMed search conducted January 2014 to identify trials in which participants received specified doses of lutein, zeaxanthin, or meso-zeaxanthin supplementation.

meso-zeaxanthin described it as being present in shrimp carapace, fish skin, and turtle fat.[18] Their report, however, did not include any details on the amount the starting material or the absolute concentration of meso-zeaxanthin found. We did our best to replicate their findings and found no presence of lutein, zeaxanthin, or meso-zeaxanthin in any fish or seafoods analyzed.

Dr Richer: If meso-zeaxanthin is not a natural dietary nutrient, what is the source of the meso-zeaxanthin found in products for ocular health?

> **I think synthetic meso-zeaxanthin should be categorized as a pharmaceutical and researched for safety and efficacy as such.** —Dr Richer

Dr Shechtman: Meso-zeaxanthin is manufactured by the saponification of lutein using a process that involves high heat and a strong alkaline environment.[19]

Dr Johnson: Because there are no natural dietary sources of meso-zeaxanthin, I consider it a misnomer to refer to synthetic meso-zeaxanthin as a "dietary supplement". A dietary supplement is something that bridges the gap for nutrients that can be obtained naturally through food sources.

Dr Richer: Anatomic distribution is another important area in which meso-zeaxanthin differs from lutein and zeaxanthin. Meso-zeaxanthin is found naturally only in the macula, whereas the dietary nutrients lutein and zeaxanthin are present in organs and tissues outside the eye such as the brain, skin, and breast and adipose tissue.[20-23]

Dr Johnson also conducted research on this subject. Please tell us what you found.

Dr Johnson: We have done studies in humans and in animal models to characterize the absorption and distribution of lutein and zeaxanthin in the body after dietary ingestion, and we also looked for meso-zeaxanthin in blood and tissues. We found lutein and zeaxanthin in the retina, blood, adipose tissue, the brain, and the skin, but meso-zeaxanthin was present only in the macula.[16,25-28]

We also have been interested in looking at carotenoid levels in the brain, based on the theory that they may have a role in cognitive development and function. Interestingly, when we looked at donated brain tissue of infants, we found lutein accounted for approximately 60% of the total carotenoids in the brain and zeaxanthin accounted for approximately 16%.[29] We estimated that together, lutein and zeaxanthin made up only approximately 16% of dietary carotenoid intake in infants; therefore, these data indicated there was preferential uptake of lutein and zeaxanthin in the brain. Zeaxanthin and lutein are found in the brain; meso-zeaxanthin has not been detected.[17,26]

We also analyzed carotenoids in donated brain tissue of octogenarians and centenarians.[25] Just as in the infants, lutein was the predominant carotenoid in the brain tissue of these older adults even though analyses of matched serum samples indicated it was not the major dietary carotenoid. In addition, we found an association between higher lutein levels in the brain and better cognitive function. We, and others, have also found correlations between better cognitive function in adults and both higher serum levels of lutein and higher MPOD scores.[25, 30-32] Consistent with those data, we showed, in a study of monkeys, that levels of lutein and zeaxanthin in the macula were significantly related to the levels of these carotenoids in brain tissue.[33] In other words, it appears that macular pigment may be a biomarker of carotenoids in the brain.

Dr Richer: There also is a major difference in terms of the volume of clinical research conducted with meso-zeaxanthin and that for lutein and zeaxanthin.

> **There is a 20-year body of robust evidence pertaining to ocular benefits of lutein and zeaxanthin from foods and supplements and supporting the safety of administering these nutrients as dietary supplements, but a relative paucity of information on meso-zeaxanthin.** —Dr Richer

Dr Gerson: A PubMed search we conducted in January 2014 identified more than 130 published clinical studies investigating lutein and zeaxanthin, more than 60 of which were supplementation studies. The first was published in 1995,[34] and together, the trials included more than 20,000 patients. In contrast, the first published human clinical study on meso-zeaxanthin supplementation appeared just 8 years ago, and there were only 8 published clinical studies, totally involving only 263 patients.[35-42] Also noteworthy is the fact that all of the meso-zeaxanthin studies were from the same group of investigators. In addition, only 2 meso-zeaxanthin studies evaluated visual

function in AMD patients,[41,43] and in all the studies, meso-zeaxanthin was always given with lutein and zeaxanthin, never alone. Therefore, it is difficult to determine to what extent meso-zeaxanthin may have contributed to the outcomes.

It is possible that meso-zeaxanthin was present in trace levels in the more than 60 lutein and zeaxanthin supplementation trials because meso-zeaxanthin can arise as an impurity during the lutein and zeaxanthin ingredient manufacturing process. However, the amount of meso-zeaxanthin in the supplements administered in those studies was never measured and therefore cannot be definitively stated as being present. Furthermore, the presence of meso-zeaxanthin in such variable, negligible amounts does not provide a basis for making any valid statements about its efficacy and safety.

Meso-zeaxanthin Fiction

Dr Richer: Proponents of meso-zeaxanthin-containing nutritional products for eye health offer several arguments to justify their use, but they are easily refuted based on a critical analysis of the evidence [**Table 2**].

One argument positions meso-zeaxanthin as a "critical macular carotenoid", and it is based on results of an in vitro study that found meso-zeaxanthin was more potent than lutein or zeaxanthin as a quencher of singlet oxygen activity.[44] There was, however, no statistical analysis of the results. A separate in vitro study reported that without the presence of their binding protein GSTP1, zeaxanthin was a more effective antioxidant than meso-zeaxanthin; their profiles were reversed in the presence of GSTP1.[45] Furthermore, there are no human clinical data on comparative antioxidant activity of the macular carotenoids, and categorically, the US Food and Drug Administration (FDA) would not accept in vitro data as sole evidence to substantiate claims about antioxidant activity in vivo.

Meso-zeaxanthin advocates are also perpetuating the idea that it is important to include meso-zeaxanthin in supplements because the ability to convert lutein to meso-zeaxanthin in the macula is lacking in some individuals.

Dr Johnson, what are your thoughts about this concept of so-called "non-converters"?

Dr Johnson: The idea that some people cannot convert lutein to meso-zeaxanthin is only theoretical, because there is no clinical evidence to validate it. Furthermore, current methods for assessing macular pigment cannot distinguish between meso-zeaxanthin, zeaxanthin, and lutein in the central macula.

Neither the mechanism for the conversion of lutein to meso-zeaxanthin nor the extent to which there is any interindividual variability in the conversion has been described, and so if there are individuals who cannot convert lutein to meso-zeaxanthin, we do not know what percentage of the population they represent or the reason why they cannot convert lutein to meso-zeaxanthin.

To my knowledge, there are no studies that have assessed the effect of meso-zeaxanthin supplementation on macular pigment in the absence of lutein and/or zeaxanthin supplementation. —Dr Shechtman

Table 2. Meso-zeaxanthin Fiction

Claim: Meso-zeaxanthin is the most potent antioxidant of the 3 macular pigments. **Response:** There are no head-to-head clinical data to support a superiority antioxidant claim. The antioxidant activity of the macular carotenoids has been compared directly in only 2 published in vitro studies and the results are not consistent. One study showed both zeaxanthin and meso-zeaxanthin quenched singlet oxygen and that the 1:1:1 combination of lutein, zeaxanthin, and meso-zeaxanthin quenched singlet oxygen better than any of the 3 pigments individually, but no statistical comparisons were made.[44] The other study investigated the antioxidant activity of zeaxanthin and meso-zeaxanthin when bound to glutathione S-transferase placental form (GSTP; their binding protein).[45] Zeaxanthin was found to be more effective when unbound to GSTP1, whereas meso-zeaxanthin was shown to be more effective when bound to GSTP1.
Claim: Meso-zeaxanthin supplementation is needed for those who cannot convert lutein to meso-zeaxanthin. **Response:** There is no published clinical evidence documenting an inability to convert lutein to meso-zeaxanthin.
Claim: Meso-zeaxanthin is needed to fill in a "central dip" (low central MPOD) in macular pigment (also called atypical macular pigment spatial profile). **Response:** Research shows that the MPOD in the center of the macula can be increased by supplementation with dietary lutein or zeaxanthin.[49]

Dr Shechtman: It has been reported that as many as 20% of people do not achieve an increase in MPOD score after starting lutein/zeaxanthin supplementation.[46] These people are deemed "low-responders", sometimes also called "non-responders". Failure to achieve an increase in MPOD could be due to a decreased ability to transport lutein to the macula. Another possible cause for the lack of MPOD score increase following supplementation of carotenoids is increased distribution of the carotenoids to adipose tissue, particularly in those who are overweight. Dysfunction in intestinal absorption may also play a contributing role.

Dr Richer: Meso-zeaxanthin is also being advocated as beneficial for filling a so-called "central dip" in macular pigment. The concept of a central dip comes from studies that identified reduced MPOD at the center of the macula, including 1 in which it was seen in 12% of subjects evaluated.[46] The investigators of that study concluded the "central dip" was an undesirable finding since it is associated with each of the following factors: older age, smoking, and AMD. Because the concentration of meso-zeaxanthin in the macular pigment peaks centrally,[48] researchers undertook a study to see if supplementation with different combinations of carotenoids with or without meso-zeaxanthin could increase central MPOD.[39]

Dr Johnson, tell us about that study.

Dr Johnson: First of all, it needs to be understood that lutein, zeaxanthin, and meso-zeaxanthin are present in a 1:1:1 ratio in the macula.[48] No single carotenoid predominates. The study to which you refer divided 31 participants into 3 groups to receive either lutein 20 mg + zeaxanthin 2 mg, lutein 10 mg + meso-zeaxanthin 10 mg + zeaxanthin 2 mg, or lutein 3 mg + meso-zeaxanthin 17 mg + zeaxanthin 2 mg: it was found that central macular pigment increased significantly only in the groups receiving meso-zeaxanthin. But the study has a number of flaws, and so it cannot be used to conclude that meso-zeaxanthin has a benefit for filling in the central dip. First, in looking at the baseline MPOD standard error values, it is not clear that the patients even had a central dip. In addition, no patients received meso-zeaxanthin alone; rather, it was always given with lutein and zeaxanthin, and that is important because we know that there is potential competition among carotenoids in terms of intestinal absorption, transport in the serum, and tissue uptake. The competitive absorption was shown in AREDS2, in which groups given beta-carotene had lower serum levels of lutein.[5]

Another criticism of the study is that the supplement products used are not identified. That information is relevant because bioavailability varies among products. Alternatively, carotenoid bioavailability could be determined based on serum levels, but those data also were not reported.

Dr Richer: Although there is meager evidence to show meso-zeaxanthin alone has a benefit for addressing a central dip in MPOD, we found in the Zeaxanthin and Visual Function Study[49] that the central MPOD improved in all 3 study groups, whether they were receiving daily supplementation with zeaxanthin 8 mg, zeaxanthin 8 mg plus lutein 9 mg, or 9 mg of lutein. Thus, these findings suggest that if there is an abnormal spatial distribution of macular pigmentation, it can be resolved with dietary zeaxanthin or dietary lutein supplementation and does not require meso-zeaxanthin.

In considering claims that there are benefits for using meso-zeaxanthin in addition to lutein to increase meso-zeaxanthin levels in the macular pigment, it also is important to realize that the studies being used to support these assertions were of short duration, usually no more than 2 months. According to my research, it can take approximately 4 months before macular meso-zeaxanthin increases when supplementing with lutein alone. Perhaps adding meso-zeaxanthin to lutein raises the macular pigment level faster. Again, however, we really do not know if that is true, because in the meso-zeaxanthin studies, meso-zeaxanthin was never given alone but rather always with lutein and zeaxanthin. Therefore, it is not possible to know which components were responsible for the macular pigment changes identified in the meso-zeaxanthin studies.

Meso-zeaxanthin Safety Issues

Dr Richer: We know from the limited clinical research with meso-zeaxanthin that its administration with lutein and zeaxanthin is associated with an increase in the MPOD score. However, these data are limited in the number of subjects and in the number of studies and their duration. Additionally, meso-zeaxanthin has never been evaluated by itself. The long-term safety of meso-zeaxanthin supplementation is not known. As stewards of our patients' long-term health, I think there is a need to be very careful in recommending any modality about which we have limited safety data.

As observed in AREDS2, the concomitant administration of beta-carotene was associated with lower lutein and zeaxanthin serum levels,[5] and it is evident from the results of studies

containing all 3 macular carotenoids that meso-zeaxanthin can reduce systemic levels of lutein and zeaxanthin by competing for their systemic absorption, especially if meso-zeaxanthin is present at high doses in the supplement.[36,40] The possibility that pharmacologic doses of meso-zeaxanthin might decrease systemic levels of lutein and zeaxanthin and/or replace these nutrients in tissues where meso-zeaxanthin is not normally found begs the scientific question, What are the potential consequences of these interactions?

Dr Hitchmoth, what are your thoughts on these issues?

Dr Hitchmoth: It seems reasonable to wonder about untoward effects of meso-zeaxanthin use, considering it is not found naturally in the diet.

The potential for unwanted effects with meso-zeaxanthin has not been evaluated yet by the scientific community, and we cannot extrapolate safety data that exist for dietary zeaxanthin and lutein to meso-zeaxanthin.
—Dr Hitchmoth

In particular, I would be concerned about the implications for brain health, given that lutein is the major carotenoid in the brain and the evidence associating cognitive function with MPOD levels and the lutein level in the brain. I have been saying for a long time that the eye is a marker for what is going on in the brain, analogous to the "canary in the coal mine", and I strongly believe that we need to know more about how use of meso-zeaxanthin affects carotenoid levels in the brain.

Dr Johnson: I agree that the eye can be a window into brain health. In addition to the evidence we have correlating macular pigment levels with brain carotenoid levels and cognitive function, we know that AMD and age-related cognitive decline share many risk factors.

Dr Richer: The occurrence of adverse skin reactions led the Directorate General for Competition Policy, Consumer Affairs, and Fraud Control (DGCCRF) in France to conduct an investigation analyzing eye vitamins on the French market. The investigation found that half the products tested contained meso-zeaxanthin that was not identified as an ingredient on the label. Instead, the labels listed only zeaxanthin, and so the products were deemed "adulterated and fraudulent".[50] The agency required French eye vitamin manufacturers to remove meso-zeaxanthin from their formulations.

There have been reports from France regarding adverse skin reactions associated with the use of eye vitamins containing meso-zeaxanthin. —Dr Richer

We know that carotenoids are present in the skin, and there is evidence associating lutein/zeaxanthin with better skin health.[53] Perhaps the explanation for the adverse skin reactions in people taking meso-zeaxanthin-containing eye vitamins is that meso-zeaxanthin was deposited in the skin, where it is not normally found. I wonder if meso-zeaxanthin use may also have adverse effects in tissues that are not visible, such as the brain.

It is clear that there are a number of unresolved issues regarding the safety of meso-zeaxanthin, including its long-term effects on other organs and its potential to interfere with lutein and zeaxanthin absorption, which do have documented benefits for health. Understanding the safety of meso-zeaxanthin will require longer-term animal and clinical studies as opposed to short-term animal studies, and the studies should include evaluation of brain metabolism and cognitive function.

Dr Ferrucci: Safety is a paramount concern when we are recommending nutritional products because patients will likely be taking them for a long time. As always, "First, do no harm".

Dr Shechtman: We need only look to the history of beta-carotene to reinforce the importance of having sufficient long-term data on safety and efficacy. Based on the thought that beta-carotene would have benefits for AMD patients, it was included in the original AREDS formulation. However, its elimination in AREDS2 had no effect on progression to advanced AMD,[5] and beta-carotene also had no effect on AMD in the Physicians' Health Study I.[52] Additionally, studies show that beta-carotene increases the risk of lung cancer among cigarette smokers or past smokers.[5,53,54]

Nutritional Guidance in Clinical Practice

Dr Richer: AREDS2 provides an evidence base for recommending supplementation with lutein and zeaxanthin for patients at risk for progression to advanced AMD. Individuals with strong risk factors for AMD, including low MPOD, represent a larger number of patients we see. Studies have shown that supplementation with lutein and zeaxanthin increase MPOD and improve visual function. In my opinion, therefore, optometrists should also be recommending the

benefits of lutein/zeaxanthin supplementation to patients with AMD or strong risk factors for AMD. Furthermore, I believe we should be measuring MPOD in these patients and recommending lutein and zeaxanthin supplementation when we feel it is appropriate based on the MPOD result. I would measure MPOD in anyone aged older than 40 years, in smokers, in obese individuals, and in those with a family history of AMD. A reasonable argument also could be made to measure MPOD in patients aged younger than 40 years, considering that harmful blue light exposure occurs throughout life and that earlier intervention to increase retinal protection by the macular pigment may be beneficial for eye health long-term.

Dr Gerson: I agree that lutein/zeaxanthin supplementation has potential benefit without any obvious risk for any adults who are not receiving enough of these nutrients in their diet. In addition, I think it is important to reiterate that lutein/zeaxanthin had benefits for reducing cataract risks in AREDS2 patients with the lowest dietary intake of lutein and zeaxanthin. Reducing cataract burden has important public health ramifications, but the cataract data in AREDS2 are often overlooked. I am unaware of any information on cataract and meso-zeaxanthin supplementation alone.

Dr Pizzimenti: The optometrist is an important resource for patients seeking to achieve optimum ocular/macular health and protection. For patients with poor dietary habits, early signs of AMD, or for those at increased risk for AMD due to genetic, personal, systemic, or environmental factors, I prescribe a supplement with appropriate levels of both zeaxanthin and lutein. A typical daily multivitamin simply is not enough for these patients.

In addition, mounting evidence suggests that AMD may be a sign of more widespread metabolic dysfunction because associations have been reported between AMD and hypertension, cardiovascular disease, cerebrovascular disease, dyslipidemia, chronic kidney disease, and neurodegenerative disorders. By taking the lead in counseling patients on nutritional intervention for AMD prevention, optometric physicians may also help these patients avoid serious complications from these other systemic conditions.

Dr Richer: Let us now talk about specific recommendations on choosing products for ocular health.

Dr Shechtman: I think it is important for patients to take both lutein and zeaxanthin because these carotenoids have different but complementary absorption spectra. Lutein absorbs the shorter blue light wavelengths while zeaxanthin is a better filter for the longer wavelengths. Therefore, taking both nutrients will optimize ocular protection, but taking 3 carotenoids is not necessarily better than taking 2.

Dr Gerson: I believe that some eye vitamin manufacturers use zeaxanthin isomers in their products for economic reasons. Generally, the synthetic zeaxanthin isomers, which contain meso-zeaxanthin, are less expensive than dietary, naturally sourced zeaxanthin itself. Patients who use a supplement containing only lutein and zeaxanthin will be getting the carotenoids that are found naturally in the diet, and the lutein ingested will increase their macular meso-zeaxanthin level through the in vivo conversion process. I think the idea of using products containing only natural dietary constituents resonates with most people. The huge difference in the amount of science that exists regarding lutein and zeaxanthin compared with that regarding meso-zeaxanthin also should influence practitioners' recommendations to patients.

Dr Richer: Dr Ferrucci, are there clinical situations in which meso-zeaxanthin should be considered?

Dr Ferrucci: I cannot think of any rationale for doing so. We have already discussed that there is no evidence to support the belief that some individuals have minimal or no ability to convert lutein to meso-zeaxanthin. Furthermore, there is no way to identify who those individuals might be. We do know that sufficient intake of zeaxanthin and lutein should adequately protect the cones and rods composing the macula,[55] and AREDS2 provides a solid evidence base for using lutein and zeaxanthin without meso-zeaxanthin. On the basis of all the available evidence, I am comfortable recommending eye supplements that contain only lutein and zeaxanthin.

Dr Hitchmoth: I am confident recommending lutein and zeaxanthin to my patients, knowing it is safe and provides proven eye benefits.

> **I keep it simple when I talk to my patients about eye supplements. The message that I use is, "Meso-zeaxanthin is not ready for prime time". There is not enough evidence showing it is helpful or that it is not going to be harmful, especially long-term.** —Dr Hitchmoth

Dr Shechtman: Of note, dietary supplements should supplement what is naturally found in the diet. Meso-zeaxanthin is known to be an enzymatic conversion that takes place in the macula.

Dr Richer: There is a consensus in the panel about recommending eye supplements containing both lutein and zeaxanthin, and avoiding products containing meso-zeaxanthin. Keep in mind, however, that some eye vitamins that list only "zeaxanthin" on their label actually contain zeaxanthin and meso-zeaxanthin, while other products list the 2 together on their label as "zeaxanthin isomers". Neither scenario accurately describes the content of those products. This constitutes considerable mislabeling because zeaxanthin and meso-zeaxanthin should each be identified as separate ingredients if they are present in the product, and their individual quantities should also be identified.

Dr Gerson, do you think this practice is causing confusion for patients who are told they should be using eye vitamins containing lutein and zeaxanthin?

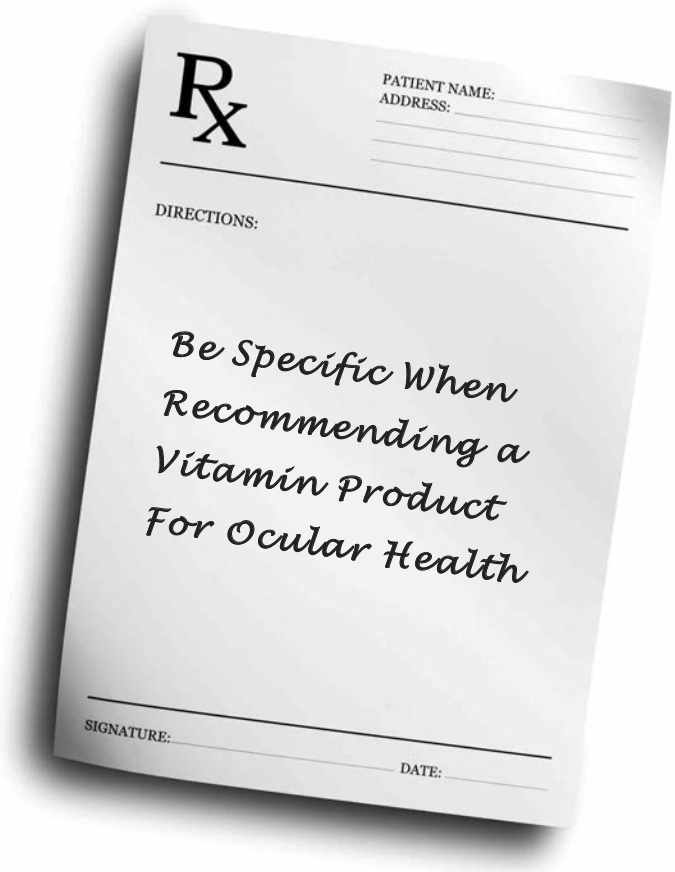
Dr Gerson: I do, because patients may incorrectly assume zeaxanthin isomers and zeaxanthin are one and the same. Therefore, it is important for practitioners to educate patients about the benefits of lutein and zeaxanthin and to instruct them to read the label carefully so that they will make the correct purchase.

Just as we are specific when writing a prescription for a medication for lowering intraocular pressure (IOP) or for any other purpose, we need to be specific in recommending a vitamin product for ocular health. In any situation, patients need to be told why a certain product is being recommended; patients should be assured that the company making these nutritional supplements is trustworthy and adheres to FDA good manufacturing standards. It is also important that the labels on these supplements accurately represent the actual ingredients in the formulation, including their respective quantities.

Dr Hitchmoth: Some practitioners feel uneasy about recommending dietary supplements, but patients look to their health care providers for such advice. When told exactly what they should take, and why, patients appreciate that they are getting information from knowledgeable professionals.

Dr Gerson: I think we need to make our clinical recommendations according to what we know from good science and make sure that our patients understand that.

The bottom line is that it is best for everyone to get the necessary nutrients by eating the right foods, but the fact is that most Americans do not always consume a proper diet, and that is why we are talking about supplements. Optometrists should be encouraging a healthy diet and recommending ocular nutrients for which there is evidence to support their use.



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