Transforming Eye Health

Through Proven Ocular Nutrition Strategies

The population is aging. More than 10,000 Americans turn 65 every day, and that will continue for the next 25 years.[1] The number of people diagnosed with age-related macular degeneration (AMD) in the United States is expected to more than double from 2.07 million to 5.44 million between 2010 and 2050.[2]

It's unknown if we have enough specialists to manage double the number of patients. No matter what, we're going to have huge dynamic shifts in optometry and ophthalmology in the United States.

We also know that younger patients may be at greater risk than previously considered. The blue light emanating from digital devices could play a significant role in changing patterns of disease development. These highly visible-light-density-type wavelengths could affect the retina and increase the risk of blindness from the early onset or proliferation of AMD.

In many cases, once AMD is diagnosed in the first eye, we manage to save the other eye the majority of the time. That means we're taking a greater interest, following the patient more carefully and looking for key signs. This inevitably prompts the question: Why didn't we do that the first time around? Why didn't we try to save that first eye, and start looking for clues at a younger age?

One strategy to combat macular degeneration is through nutritional supplementation. AREDS2—published in 2013—is the largest study completed on the impact of nutritional supplements on AMD progression with various cohorts.[3] Since then, other significant studies have helped us further understand the role diet and nutritional supplements play. How can we reduce the risk of disease emergence and progression?

We put together an esteemed panel at Vision Expo West 2015 to discuss this issue in a way that will aid clinicians in their management of macular degeneration and understanding of the role of nutritional supplements.

– Paul M. Karpecki, OD, FAAO

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AREDS2 Revisited: The Third Carotenoid

Dr. Karpecki: *In the AREDS2 study design, there was a belief that the addition of macular carotenoids, such as lutein and zeaxanthin, may aid in reducing the risk of disease progression. At the time, meso-zeaxanthin was not well-known. Since then, what have we learned about the role of meso-zeaxanthin?*

Dr. Beatty: AREDS2 showed us that supplementation with some macular pigment carotenoids does reduce the risk of disease progression and visual loss if you have non-advanced AMD. However, there were two problems with the AREDS2 study. First, the study formulation had high levels of zinc; some papers have since come out suggesting that, for certain AMD patients with a specific genetic background, the high levels of zinc in AREDS2 cause disease progression.[4] Second, there are three components to macular pigment: lutein, zeaxanthin and meso-zeaxanthin. All head-to-head trials have shown that including meso-zeaxanthin not only increases macular pigment centrally, where you most need it, but also enhances visual performance in patients who have early AMD.[5,6]

Dr. Sherman: I, and perhaps many others, started to pay close attention to meso-zeaxanthin when an article titled "Targeting AMD with a Critical Carotenoid" was published in *Review of Ophthalmology* in March 2011.[7] The paper was authored by arguably four of the world's experts in this area: Drs. Richard Bone, John Landrum, Stephen Beatty and John Nolan. The critical carotenoid identified was meso-zeaxanthin. Since I read that article, there have been some very important studies published with similar findings and conclusions.

Need for Meso-Zeaxanthin Supplementation

Dr. Karpecki: *One question that comes up around meso-zeaxanthin concerns its origin. Isn't it wholly derived, or could it be wholly derived, from retina lutein? And in a related point: Is there a need to supplement meso-zeaxanthin?*

Dr. Renzi-Hammond: I think that all of us would love to live in a perfect world, one where we advocate letting 'food be thy medicine and medicine be thy food.' If you can eat a sufficient amount of healthy food, that is ideally where you should be getting these dietary components. Where meso-zeaxanthin is concerned, if our general populous is not able to get enough basic lutein and zeaxanthin out of their diets, we're really sort of reaching if we believe they're going to go out and eat enough fish skin, for example, to acquire this byproduct of a molecular conversion. There is a pretty strong consensus that suggests meso-zeaxanthin is made from lutein, but one thing that we are absolutely unclear on with respect to carotenoid biosynthesis is whether all members of the population are able to conduct this conversion appropriately. Dietary supplementation with something like meso-zeaxanthin is going to be the only way to achieve the necessary levels unless you're relying on your own biochemistry to do the job. For most people, that's enough, but likely not for all.

Dr. Beatty: In a recent study, we showed meso-zeaxanthin is in trout flesh and a few kinds of fish skin, but these are not typical dietary staples.[8] I agree with Dr. Renzi-Hammond—there is a consensus that retina meso-zeaxanthin is derived in part from retina lutein. This is based on two older studies: one in primates and one in

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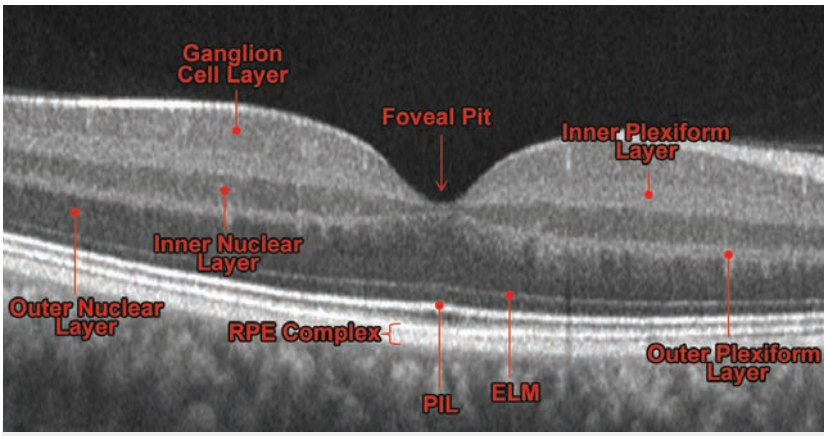
quails.[9,10] However, is it not true that all retina meso-zeaxanthin is derived from retina lutein? If you look at the quail study, the lutein only accounted for 50% of the meso-zeaxanthin found. Also take into account Paul Bernstein's research, which shows that you need all three macular carotenoids present in a 1:1:1 ratio to exert maximum antioxidant effect.[11] The lutein supplement given to the animals in the above studies probably contained some meso-zeaxanthin that researchers were unaware of, accounting for part of the meso-zeaxanthin detected. I think those studies really do need to be revisited. Even just two years ago, Dr. Karpecki's question would have been put very differently; we would have been much more affirmative that meso-zeaxanthin is derived from lutein. That's now been questioned. I suspect meso-zeaxanthin does derive, in part, from lutein in the retina. But, as Dr. Renzi-Hammond says, if it can be delivered prepared and pristine without any bioconversion necessary, which perhaps not all people can achieve, wouldn't that be the sensible thing to do?

Photo by: Jerome Sherman, OD



In the eye, high concentrations of meso-zeaxanthin are contained within, and immediately around, the foveal pit, as visualized here by OCT.

Dr. Karpecki: *Do you have anything to add on the role of meso-zeaxanthin in the macula itself, its central location or its high concentration?*

Dr. Sherman: It appears that meso-zeaxanthin is found pretty much in one place, towards the center of the fovea. For some reason it's there, and it must have a purpose. Hence, if we want our fovea to work, it seems like we want a high level of meso-zeaxanthin, either in a diet or added as a supplement.

> *"Where meso-zeaxanthin is concerned, if our general populous is not able to get enough basic lutein and zeaxanthin out of their diets, we're really sort of reaching if we believe they're going to go out and eat enough fish skin, for example, to acquire this byproduct of a molecular conversion."* — Dr. Renzi-Hammond

Lutein Absorption & the Literature

Dr. Karpecki: *The AREDS2 study results showed that beta-carotene actually inhibited the absorption of carotenoids like lutein and zeaxanthin in the cohort receiving carotenoids with beta-carotene. We've also heard that meso-zeaxanthin may inhibit the absorption of lutein because it's similarly a carotenoid. What are your thoughts on this, and are there any recent studies that validate your opinion?*

Dr. Beatty: In a study we just published in *Eye*, three groups of patients, all with early AMD, were supplemented with 20mg of lutein, 2mg of zeaxanthin and a few undeclared nanograms of meso-zeaxanthin vs. the MacuHealth formulation—which

is 10mg of lutein, 10mg of meso-zeaxanthin and 2mg of zeaxanthin—vs. very high meso-zeaxanthin.[12] What was amazing was the serum lutein response was just as high in those supplemented with 10mg of lutein and 10mg of meso-zeaxanthin when compared with those supplemented with 20mg of lutein. In other words, supplemental meso-zeaxanthin did not inhibit the gastrointestinal absorption of lutein whatsoever. And we're talking about serum response, so there's no ambiguity here.

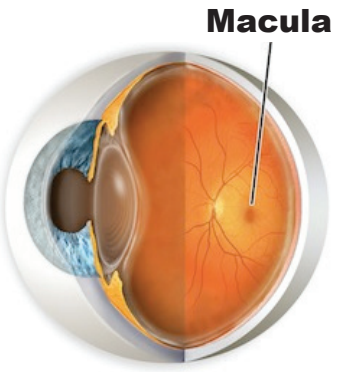
Dr. Renzi-Hammond: We've known for a very long time that high doses of beta-carotene will inhibit absorption in the gut. This is not something new to us. It's been an issue since the 1990s, when papers came out that documented this effect.[13-16]

Carotenoid Improvements on Macular Pigment

Dr. Karpecki: *What are the most important foods we should be telling our patients to consume to get the greatest carotenoid benefit from diet, and is that sufficient, or is the key really additional supplementation?*

Dr. Renzi-Hammond: Let's take our best-case scenario. We have a well-nourished patient who is eating a healthy diet, rich in fruits and vegetables, whole grains, fatty fish, and is low in dietary sources of saturated or trans fat. We like to believe that is enough, and for those who are otherwise leading a healthy lifestyle, it very well might be. One thing that is likely true is that the nutritional content of food is simply not what it was a long time ago. Foods are now frequently genetically modified, soil quality has changed, and we are exposed to a number of oxidative stressors, endocrine disruptors and other less-than-optimal chemical compounds we were not exposed to in the history of our species. The other issue to consider is that even a good diet is not a magic bullet. All things that we ingest are going to be better absorbed or more poorly absorbed depending on other factors present. An individual with high body fat percentage, for example, who might be trying to eat decent food but is not exercising, is potentially going to be storing a lot of these carotenoids in fat depots in the body and not absorbing what they should. We have the convenience diets that most of us rely on; 60% of the food we eat in the United States is processed. So, supplementation is becoming more necessary, given our lifestyles.

Dr. Beatty: I want to echo everything Dr. Renzi-Hammond said. What is interesting is if you take a room full of well-fed people who have good diets and you supplement them, their macular pigment increases. And an increase in macular pigment does enhance your visual performance. A healthy diet rich in fruits and vegetables is absolutely fine, but we're living so much longer than we used to. Whether or not we need to supplement as a matter of routine to give us the tissue concentrations of certain nutrients to allow us to age gracefully



and healthfully is the question. There's no evidence base to say you can get enough from your diet through your 80s because we've only been living to our 80s for 20 years.

Dr. Sherman: Findings from the CREST study may shed light on this issue.[17] Starting with seemingly normal individuals who had relatively low levels of the three carotenoids in their serum, with "lowish" macular pigment levels.

Dr. Renzi-Hammond: About 10 years ago, when my collaborators measured the optical density of the pigment, they found the average in the United States was right around 0.3.[18,19] We're in the process of completing a study looking at young, "healthy" adults, college students clicking away on

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researchers supplemented this group with lutein, zeaxanthin and meso-zeaxanthin, and demonstrated macular pigment improvements. However, it's simpler to show a change in subjects with relatively low levels of the carotenoids than it is to look at those who have very healthy diets and high carotenoid levels.

Dr. Beatty: In that study, we were afraid of having a ceiling effect, so we purposely chose subjects who had macular pigment of 0.5 or less. I think Dr. Renzi-Hammond would support me here in saying 0.5 isn't that low. We're not saying only people with appalling diets need supplementation, but also those all cylinders cognitively; and older adults—those aging well, and others manifesting signs of mild cognitive impairment. One finding that was sort of shocking: In the young, healthy adults who should not have been able to improve very much, as soon as retinal levels of these carotenoids began to change, we saw corresponding changes in cognitive function.

Dr. Beatty: The point Dr. Renzi-Hammond just alluded to is that having high levels of macular pigment does not mean you won't benefit from supplements. Even with a baseline score of 0.8, one can't assume that going up to 1.3 won't help; it does. We chose subjects who were

The Zinc Paradox

Dr. Karpecki: *Is there anything to the concern that some zinc oxide supplements may use greater than the recommended dietary allowance (RDA) level or a non-oxide version?*

Dr. Sherman: The National Eye Institute still continues to recommend 80mg of zinc per day even though the AREDS2 study demonstrated no difference between 80mg and 25mg. Does that make any sense? I think it makes sense to virtually no one and yet that's what many of us are still doing. In the AREDS1 study, the comparison was 80mg of zinc vs. 0mg. For those patients with a specific genetic profile—14% to 19% of the population—who were taking 80mg of zinc, many actually got worse. There's mounting evidence that 80mg of zinc is doing a lot of harm to at least that subgroup of people. So, dosage is critical. Paracelsus, the father of modern toxicology, noted more than 500 years ago that the right dose differentiates a poison and a remedy. And when the recommended daily allowance is about 10mg, why should we ever consider going to 80mg of zinc?

Dr. Beatty: If you go to the website of the Office of Dietary Supplements of the National Institutes of Health, you will see the RDA is 8mg for a woman and 10mg for a man, and the upper tolerable level is 40mg. In other words, 80mg is too much. It would seem to me that from a legal perspective—forget for a moment the scientific basis—you're exceeding the recommended dietary allowance. It just would seem counterintuitive to me to do that, which is why I use a formulation that contains 25mg of zinc.

The Optometrist as Neuroscientist

Dr. Karpecki: *Can you comment on the link between macular carotenoids and cognitive function?*

Dr. Renzi-Hammond: The retina is a wonderful prognostic indicator of what's going to happen to the rest of the central nervous system. When you see signs of hypertension, your patient might not have been diagnosed as hypertensive yet. When you see optic neuritis not linked to ocular disease, you're the first person who's going to be able to tell that patient, 'you need to go see a neurologist.' And, in my view, when we detect evidence of age-related macular degeneration, we might be also seeing signs of Alzheimer's disease. Eye care professionals, to me, are the one health care providers regularly looking at the central nervous system, with some ability to predict how the rest of the central nervous system is going to go. Dr. Beatty's group and my team have done studies where we have supplemented macular carotenoids and seen improvements in cognitive function. Other sites like the University of Illinois at Urbana-Champaign and Tufts University in Boston have seen the same thing. There's a confluence of evidence.

Dr. Beatty: We were involved in the Irish Longitudinal Study on Aging, and we measured macular pigment as well as the results of 12 tests of cognition on 5,000 subjects over 55 years of age.[20] Eleven of those 12 tests related positively and significantly to macular pigment levels. In other words: The more pigment you have at the back of your eye, the better your cognition.

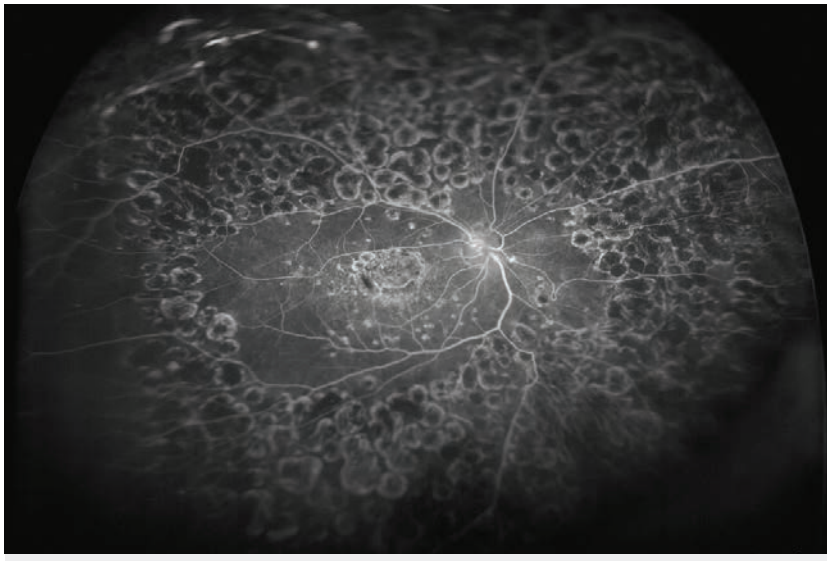


Photo by: Optos

Patients with type 2 diabetes are at an elevated risk for diabetic retinopathy and macular edema, as seen here on fluorescein angiography. Lifestyle changes, dietary alteration and nutritional supplementation can help limit the development and progression of diabetic eye disease.

at 0.5 or less, and those given MacuHealth vs. the placebo exhibited improvements in visual function, especially contrast sensitivity.

Prevention Strategies

Dr. Karpecki: *Why would young, healthy patients with good vision want to maximize macular pigment?*

Dr. Renzi-Hammond: We focus a lot on the population that already has a condition, and we sort of ignore what's going on in the 75 years leading up to that state. Then we assume that we can intervene with nutrition and actually have some success. We're lucky to be in a field—vision science—where we can make a difference in a patient with disease. For the most part, though, the bulk of where we should be spending our energy is before they ever get to that point, to make every effort at prevention.

Dr. Sherman: Something else to think about: When does age-related macular degeneration begin? One could argue that it begins in utero because your genetic profile is already set. Age-related macular degeneration may start at age 0 and not really affect the patient until they are 65, 70 or 75.

Dr. Beatty: I firmly believe the reasons for supplementation in young people is twofold: one, for visual performance enhancement, which is demonstrable

within months; and two, to protect against long-term chronic and cumulative damage, which cause AMD and contribute to Alzheimer's disease.

Role of Ocular Nutrition in U.S. Healthcare

Dr. Karpecki: *Looking at the U.S. system of overall healthcare, ACOs, the evolving role of optometry and the shortage of surgeons in ophthalmology, can you discuss what ocular nutrition means to the future of healthcare?*

Dr. Sherman: We do have some responsibility for the overall health of the patient. The vast majority of type 2 diabetes is completely preventable, and yet it's going to not only cause blindness and a multitude of deaths, it's going to bankrupt our entire healthcare system if we don't get a handle on it. The optometrist is in the position to play a role in preventing macular degeneration, and also diseases like diabetes that are much more common in the entire population.

Dr. Renzi-Hammond: One thing we know is that when we start giving adults in the hospital oral nutritional supplements, readmission rates drop. The healthcare system spends less when we care about nutrition, and that's just with respect to critical care admissions. Right now, pharmacology is in many cases cheaper than nutrition, so if we could start looking at what we would save—the health economics of giving people better nutrition—then we would be in a much better position where prevention is concerned. I also feel that for a lot of folks in financial hardship, if you're working three jobs, poor nutrition doesn't stem from laziness or lack of awareness. The patient's mindset is not, 'I don't know that I should eat this food' but rather, 'I don't have the money, and I don't have the time.' If we can start nutritionally supporting this group of people in a different way, we're helping the percentage of the population that is most likely to get these sorts of degenerative diseases.

Dr. Beatty: We also need to talk about how to help the optometrist. Their practice revenue model has historically relied on refraction and corrective lenses. But optometrists are both vision specialists and *eye* specialists. If they want to avoid being squeezed by the ever-reducing cost of Internet sales, if they want to make a space for themselves that won't be occupied by busy ophthalmologists, this is the space: macular pigment and how it relates to visual function and brain function.

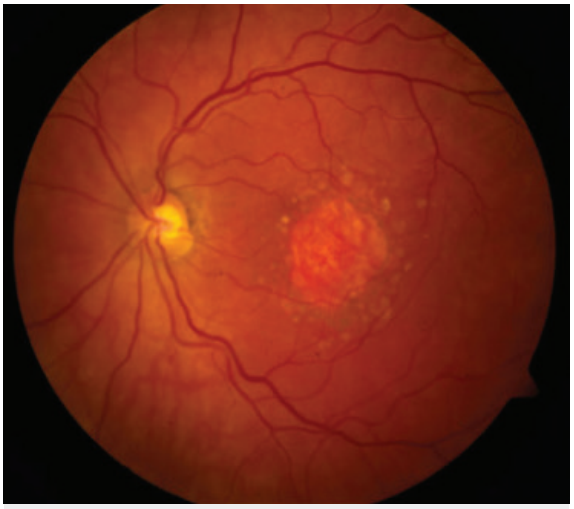
> ***"Optometrists have to start to feeling comfortable talking about lifestyle changes. An obese patient sits in the chair: They can't ignore that. Somebody who hasn't exercised in the last 12 years: They can't ignore that either. Patients can live a long life, in many cases, just by controlling lifestyle choices. And some of them are making terrible choices. Most ODs don't want to touch that, but they should."*** — *Dr. Sherman*

Talking to Patients

Dr. Karpecki: *What do I need to have at the tip of my fingers when reviewing ocular nutrition with patients who have macular degeneration or disease, and those who don't?*

Dr. Sherman: Optometrists have to start to feel comfortable talking about lifestyle changes. An obese patient sits in the chair: They can't ignore that. Somebody who hasn't exercised in the last 12 years: They can't ignore that either. Patients can live a long life, in many cases, just by controlling lifestyle choices. And some of them are

Photo by: National Eye Institute



Multiple clinical trials have indicated that nutritional supplementation with dietary carotenoids, particularly meso-zeaxanthin, can improve contrast sensitivity and enhance overall visual performance in patients with early age-related macular degeneration, as seen here.

making terrible choices, unfortunately. Most ODs don't want to touch that, but they should.

Dr. Renzi-Hammond: We need to understand how to be prescriptive. I know that if I can get my 90-year-old research subject to start lifting weights, she will beef up her bone mineral density and get a little bit of brain-derived neurotrophic factor, she'll grow some new neurons. How do I tell a 90-year-old woman to go pump some iron? If I just tell her, 'You need to go exercise,' she is probably not going to join a gym. We need to give our eye care professionals prescriptive tools: Optometrists should be able to say, 'Here's what you need to achieve in ocular nutrition: Take this daily with a meal. Here is a list of vegetables that are good for your eyes. Eat at least three a day.' Patients understand better how to change their behavior when instructions are clear, rather than the vague suggestion of, 'improve your diet.'

Dr. Beatty: I tell patients that supplementation has three roles in terms of the eye: one, to optimize your visual performance regardless of your age; two, to reduce the risk of progression of macular degeneration and potential vision loss; and three, to prevent disease. We know there is a lack of macular pigment decades before the onset of disease. But what I say, and it's borne out by AREDS2, is that this is not hypothetical; this is no longer a theory, this is a fact. It is good for you; you need to take these supplements. ■

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