A Supplement to REVIEW OF OPTOMETRY

WELLNESS ESSENTIALS
FOR CLINICAL PRACTICE

2nd edition

Follow these principles to encourage disease prevention and healthful living among your patients.

Content by OWNS | OCULAR WELLNESS & NUTRITION SOCIETY

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WELLNESS ESSENTIALS
FOR CLINICAL PRACTICE

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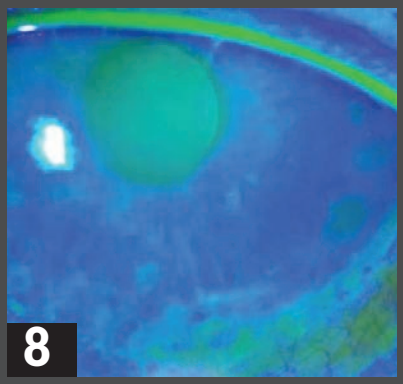

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Dr. Davey is a tenured professor at Western University of Health Sciences College of Optometry, with particular interest and expertise in glaucoma. He has authored over 50 international publications and given over 200 conference and invited presentations. He is an active researcher in ocular and vision sciences for both the NIH and industry.

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Ms. Cline has diverse experience in community education, corporate fundraising and non-profit board governance. She has worked for nearly a decade in non-profit leadership, lobbying and event management. Her background is in environmental chemistry and laboratory quality assurance.

Be a Part of the Vanguard

Focus on ocular wellness before disease sets in.

FROM THE BOARD OF THE OCULAR WELLNESS & NUTRITION SOCIETY

All day long, you see patients and strive to do the best you can for them in the limited time you have. For those with vision or eye health concerns, you diligently explain treatment options, monitoring schedules and referral paths if necessary. For healthy patients, however, you probably just send them on their way with a reminder about their next exam in a year's time.

Both of these groups, but especially the latter, need a little more attention, if you can spare it. The best way to 'treat' disease is to avoid it in the first place.

In an age of ever-increasing competing priorities, what could be of greater importance than optimizing the ocular and visual welfare of your patients? While eye care professionals are exceptionally busy today, it's critical to remember that preventive medicine and the ongoing repair and maintenance of ocular tissue should be at the core of primary eye care practice. Taking steps to monitor patients' eye and vision health early and frequently, and educate patients about key wellness and nutritional strategies, are essential steps in helping prevent degenerative diseases and pathology, prompted not only by the aging process but also by unhealthy lifestyle choices.

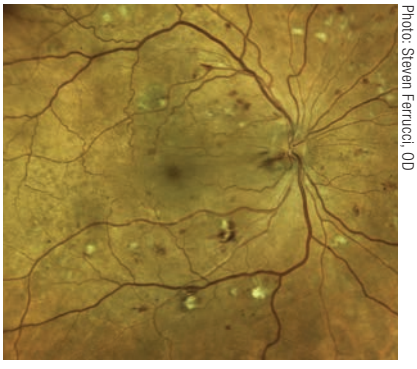

Photo: Steven Ferrucci, OD

Diabetic retinopathy is just one condition optometrists are vital players in managing—and, ideally, preventing.

PRIMARY EYE CARE LAGS BEHIND

A 2019 study in *The Lancet* showed that, globally, one-fifth of all deaths, or 11 million mortalities, were associated with poor diet.[1] In the US, 63% of all food consumed has been found to be processed, with only 12% of food coming from plant sources; the remaining 25% comes from animal sources.[2] At OWNS, we believe that minimizing processed, manufactured food and exchanging it with whole, organic food is the single most important factor in improving ocular and overall health through reducing inflammation—the core component of all chronic disease. At the same time, researchers have found that higher fish and nut consumption is associated with a lower risk of AMD progression among subjects in certain settings.[3]

Unfortunately, optometry and medical schools are not evolving to reflect a changing wellness landscape. Their philosophies and curricula continue to center upon symptoms-based medicine rather than addressing root causes. OWNS is committed to raising the awareness of practicing health providers to counteract this outdated approach to eye care and medicine. The mission of OWNS is "to provide leadership, education, advice, and guidance to eye care and other health care professionals and consumers regarding the role of lifestyle choices and nutritional support as it relates to vision and eye health. The OWNS supports evidence-based analysis concerning nutritional influences on eyes and systemic disease."

As our mission spells out, the society supports evidenced-based information. And we disseminate this scientific guidance in a variety of ways to help health care providers make the best decisions for their patients, with the goal of better patient outcomes and elevated doctor-patient relationships.

Q&A With a CNS Optometrist

***Dr. Gioia,** owner of Integrative Vision, Shrewsbury, NJ*

Neda Gioia, OD, an independent optometry practice owner and student in the OWNS Certified Nutritionist Specialist (CNS) program, shares her experiences going through the CNS program, and making nutrition and health a major focus for the last five years of her life.

Can you explain how nutrition and wellness became so important for you in general and how it's intersected with your optometric life?

I always thought of myself as healthy, but I was exposed to something that was very unhealthy, which devolved into a neurological condition. That led me to seek other avenues of trying to treat myself. So I was ready to start implementing nutrition and functional medicine into my own life. And that drive surpassed the desire of just trying to learn something for knowledge; it became personal.

As an optometrist who deals with primary care, I thought it would be a loss for my patients if I didn't expose them to what I've learned. That's when I started researching how I could bring the areas of wellness, nutrition and functional medicine into optometry vs. having it be a completely separate entity.

You are working your way through the OWNS CNS program clinical hours under the supervision of another CNS mentor. What has your experience been like with the CNS program? Did you learn anything that surprised you, going through the program?

My experience with the CNS program has been wonderful in the sense that it's so organized, and the courses have been so enlightening and so in-depth. The program really put me on a different level of understanding about the core concepts of nutrition.

There were surprises throughout the program. My biggest surprise was with the gut microbiome. Many companies are trying to tap into research findings about the microbiome to treat a lot of chronic health conditions, and even eye conditions are being studied.

How do you think the CNS program will benefit your patients and practice into the future?

Any patient who walks in the door of an optometry office where the doctor has exposure to nutritional education such as from the CNS program is in better standing. That patient's likely not getting this information anywhere else in their medical consultations. Therefore, we're going to stand out as an impactful subspecialty of the medical world that can introduce these patients to a different way of treating their health concerns. This is medicine of the future, and we have an opportunity to help lead.

You also completed the first module for The Institute for Functional Medicine recently. What is driving you to seek additional credential opportunities in the areas of nutrition and functional medicine relative to your optometric practice?

When I was investigating different programs for nutrition, The Institute of Functional Medicine always popped up. The program really gears toward medical doctors. And when I first applied, the admissions staff rejected me because I was an optometrist. I wrote them a long letter making my case for why I should be admitted. Nothing happened, and a year later I found out that the Ocular Wellness & Nutrition Society had gotten them to accept qualifying optometrists. I reapplied and was accepted, so I finished the main module on implementation. That is why I decided to go even further—to learn how to implement functional medicine in my practice.

You have noted the unique nature of your office. Can you explain what you mean, relative to the discipline of human nutrition and functional medicine in optometric practice?

We currently are in a launch phase. I always wanted to have an optometry practice with a nutrition program weaved in. And that's what I decided to do with this office—not have nutrition just as a side program, but actually as a highlight. In addition to protocols for patients who want to go through my nutrition program, I have laboratories that I'm working with to do special diagnostic tests, and I implemented an antioxidant tester.

I also have a standby coach to help me complete the programs for patients. If you want to do a full program, it takes a lot of time between the lab work and creating protocols for the patient, which you have to keep adjusting. We're going to have all the primary care services that a primary care optometry office has, but for the patients who have chronic conditions—which unfortunately now is more the norm—they can see that we offer wellness advice and would like to help them with their issues. If they are comfortable with that, maybe they'll want to seek more help in the world of nutrition.

My other motivation for having a dual functioning practice model was to figure out how to put it front and center as a business model. With the time that you spend to do all of this, colleagues are going to ask why, and if you're not able to show them how to incorporate nutrition into the practice, they will have a hard time deciding to go forward with a similar program. That's why I want to prove the model. I would like to create a way to help counsel other health care providers on how to do it in the future, too.

Do you think that more practices around the country will be seeking to become credentialed in the areas of nutrition and functional medicine relative to your optometric practice in the future?

Absolutely. Today's patients are asking more questions. They want to know, 'What other options do I have? What can I do?' And they're used to answers like, 'Well, it is what it is.' But that's not how we should be treating our patients. We should empower them, and we should walk side by side with them to try to find answers, or help them in other avenues that intersect. Younger providers are also asking questions. They are much more exposed to the concept of health change and wellness; that philosophy is now out there in the media. I think, going forward, they want change, too. And the CNS program provides that change.

BE A PART OF THE VANGUARD

The CNS Curriculum

Optometrists who pursue the Certified Nutrition Specialist program will undergo the following courses:

- MSN 6200 Nutritional Biochemistry (offered Spring and Fall)
- MSN 6101 Evidence-Based Nutrition (offered Summer and Winter)
- MSN 6305 Whole Food Nutrition and Supplementation (offered Summer and Winter)
- MSN 6204 Gastrointestinal Imbalances (offered Spring and Fall)
- MSN 7215 Cardiovascular Disease and Metabolic Imbalances (offered Summer and Winter)
- MSN 6300 Detoxification and Biotransformation Pathways and Imbalances (offered Summer and Winter)

Totals: 18 quarter-credits (4.5 quarter-credits biochemistry, 13.5 quarter-credits nutrition).

Tuition, determined by the UWS Board of Trustees, is $473 per credit. OWNS members receive a 15% discount. See www.ocularnutritionsociety.org/become-a-cns for more.

GET INVOLVED—AND EVOLVED

Wellness efforts can range from a simple, quick conversation with an AMD or prediabetes patient about lifestyle modifications to a full-blown commitment to embracing the principles of preventive medicine with additional formal training. In short, there's a way forward for everyone. Below are some of the things you can do to adopt a wellness mindset in your practice.

1. Join OWNS. Optometrists who join the society set themselves on a path to learn fundamental and advanced concepts in wellness, build a network of like-minded colleagues to seek out as mentors and begin to apply these principles in their practices. This is a vital first step.

2. Earn an OWNS Fellowship. To further its mission, OWNS offers a fellowship program for candidates seeking to be credentialed at the highest level of professional competence. Individuals have up to five years to complete the process. Retroactive nutrition-related hours for the past three years can be applied toward the total education requirement. The Fellowship Committee works with candidates to develop materials that demonstrate eligibility to sit for the oral exam. The qualification process is designed to help candidates develop as professionals and successfully become fellows through a four-step process that includes a validated application, attainment of 150 CE hours, completed written documentation and a passing oral exam. Learn more about this esteemed designation here: www.ocularnutritionsociety.org/fellowship-program.

3. Become a Certified Nutrition Specialist. Recently, OWNS, in collaboration with the University of Western States, developed an online course suite enabling qualified optometrists to sit for the Certified Nutrition Specialist (CNS) Examination. The CNS certificate is held by clinical nutritionists, physicians and other health professionals with a specialty in nutrition. It is the only non-dietetics credential and examination widely respected in state nutrition licensure laws. Thus, optometric CNS certification monetizes ocular health promotion, for your private pay and some insurance carriers. It is a model for the future of eye care that OWNS hopes will be adopted by the AOA.

OWNS Liaisons at Optometry Colleges

School	Location	Faculty Advisor	Faculty email
Illinois College of Optometry	Chicago, IL	Stuart Richer, OD, PhD	stuart.richer1@va.gov
Indiana School of Optometry	Bloomington, IN	Julie Torbit, OD	jtorbit@indiana.edu
Midwestern University	Downers Grove, IL	Diyana Ivanova, OD	divano@midwestern.edu
Nova Southeastern University	Ft. Lauderdale, FL	Lori Vollmer, OD	lvollmer@nova.edu
New England College of Optometry	Boston, MA	Diane Russo, OD	russod@neco.edu
Pacific University College of Optometry	Forest Grove, OR	James Kundart, OD Dina Erickson, OD	kundart@pacificu.edu derickson@pacific.edu
Southern College of Optometry	Memphis, TN	Taylor Kiser, OD	tkiser@sco.edu
SUNY College of Optometry	New York, NY	Jerry Rapp, PhD	jrapp@sunyopt.edu
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University of Houston College of Optometry	Houston, TX	Bruce Onofrey, OD, RPh	beonofre@cetral.UH.edu
University of Missouri at St. Louis	St. Louis, MO	Mary Beth Rhomberg, OD	rhombergm@msx.umsl.edu
Western University College of Optometry	Pomona, CA	Pinakin G. Davey, OD, PhD	pdavey@westernu.edu

4. Join the Academy's SIG. Other educational efforts in nutrition, conducted by many members of OWNS, happen through the American Academy of Optometry's Nutrition, Disease Prevention & Wellness special interest group (SIG). The mission of the SIG is to promote excellent patient care with lifestyle and nutritional support for prevention and management of eye diseases and related systemic disorders through professional education, scientific investigation and multidisciplinary collaboration. The group strives to foster camaraderie and mentorship for students, doctors and researchers interested in nutrition science and wellness as it relates to eye care.

5. Get connected locally with an OWNS liaison. Optometrists currently in practice and those students now joining the ranks can reach out to an OWNS representative at their local college of optometry. The society is in the process of appointing an OWNS liaison at each of the colleges to serve as a resource. Go to the society's main website for information and updates: www.ocularnutritionsociety.org.

THE FUTURE OF WELLNESS

It is the intention of our society to create self-funded, sustainable preventive ocular health and wellness clinics at optometry colleges. We envision each clinic to consist of three divisions:

(1) Ocular/vision/systemic evaluation, including macular pigment optical density, three-channel color vision and systemic antioxidant status.

(2) An educational center with finger blood spot/saliva/urine biomarker self-assessment.

(3) An apothecary of nutritional and pharmaceutical offerings.

Actionable testing would include, for example, predictive epigenetic biomarkers such as genetic testing for AMD, celiac and hemochromatosis diseases (for more, see the article by Russel Jaffe, MD, PhD, in the 2018 edition of this supplement at www.reviewofoptometry.com/publications/wellness2018). Home testing would include, for example, 25-OH vitamin D liver reserve status, RBC EPA/DHA cellular membrane essential fatty acid status, early morning urine pH magnesium and potassium status, high-sensitivity (hs)-C-reactive protein (CRP) inflammatory status and other broad biomarkers of health. In addition, devices to measure macular pigment optic density and skin carotenoid concentrations would be available.

This is one half of our dream; the other half is credentialing as many optometrists with the CNS designation as there are practicing ODs. We hope you consider becoming a part of OWNS and stepping into our bright wellness vision of the future. ❍

OWNS on the Move

It's an exciting time to be a member of OWNS. Here are some of the latest goings-on:

• Julie Poteet, OD, CNS, vice president of OWNS, is now overseeing our *Weekly Wellness Spotlight* email to members, which offers relevant information from the preventative medicine landscape around the country and beyond.

• Our fall 2018 Pre-American Academy of Optometry meeting in San Antonio featured Barry Tan, PhD, founder of American River Nutrition and one of the world's foremost experts on vitamin E. Dr. Tan discussed the ability of vitamin E isomers (tocotrienols) to mitigate chronic conditions, including ocular disease.

• Our 12th Annual Ocular Wellness and Nutrition Meeting was held at the University of Missouri, St. Louis College of Optometry April 13 to 14, and featured spirited lecture topics such as energy medicine and environmental influences on myopia. Keynote speaker Dan Winter, an international energy medicine expert, was featured via a video link from Paris. Also presenting was Don Mutti, OD, PhD, Janis Eells, PhD, Julie Dekinder, OD, and Stuart Richer, OD, PhD To view these presentations, go to www.ocularnutritionsociety.org/meetings.

• As retiring OWNS Board member Elizabeth J. Johnson, PhD, one of the world's experts in carotenoids, steps down after years of dedicated service, we welcome two new highly accomplished board members:

Dr. Davey

Dr. Aggarwala

—*Pinakin Davey, PhD, OD, FAAO*, director of research at the Western University College of Optometry in Pomona, Calif., brings a strong statistical medicine background.

—*Karan R "Gregg" Aggarwala, PhD, FAAO*, a nutritionist and vision scientist at InVite Health, and a protégé of researcher-author Benjamin Clarence Lane, OD, MPH, FAAO, FCOVD, is focused on eye care research, education and instrumentation.

• Many optometry schools now have active student OWNS chapters. The UAB student chapter was recently featured in our *Weekly Wellness Spotlight*. We believe the future of the society will be bolstered and promoted by students raising awareness about ocular health and overall wellness.

• This supplement, produced for the second year in a row in partnership with *Review of Optometry*, was made possible by an unrestricted grant from Bausch + Lomb.

1. GBD 2017 Diet Collaborators. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2019 May 11;393(10184):1958-72.
2. USDA Economic Research Service. U.S. Food Consumption as a % of Calories. 2009. Available at: https://www.healthyschoolfood.org/docs/color_pie_chart.pdf. (last accessed September 3, 2019).
3. Seddon JM, Cote J, Rosner B. Progression of age-related macular degeneration: association with dietary fat, transunsaturated fat, nuts, and fish intake. Arch Ophthalmol. 2003;121(12):1728-37.

The Nuts and Bolts of Nutrients

Eyes and bodies need a balanced diet rich in vitamins and minerals. Here's how you can recommend healthy eating habits and appropriate supplementation.

BY STUART RICHER, OD, PhD

Most Americans don't eat enough vegetables, fruits and other nutrient-rich foods, given the current rate of obesity—40%, as last reported by the CDC.[1] Not only do poor food choices and high-calorie, low-nutrient alternatives literally weigh on Americans, they can also be harmful to the eyes, vision, cognition and other critical systems in the body.

It's been said that vitamin deficiency is indistinguishable from radiation damage when examining cultured cells in a petri dish. Vitamin and mineral deficiency is boosting the incidence of age-related diseases, including a number of ocular diseases such as age-related macular degeneration (AMD) and diabetic retinopathy.

Our patients can improve their wellness by making proper vitamin and mineral intake a goal rather than an afterthought in their lives. But how can you help them make the right choices? With dozens of nutrients playing a part in human health—each with specific mechanisms and dietary sources—keeping up with the relevant effects can be intimidating even for doctors. This guide highlights a few key concepts for each, out of a vast body of nutritional knowledge that all doctors would do well to understand more deeply.

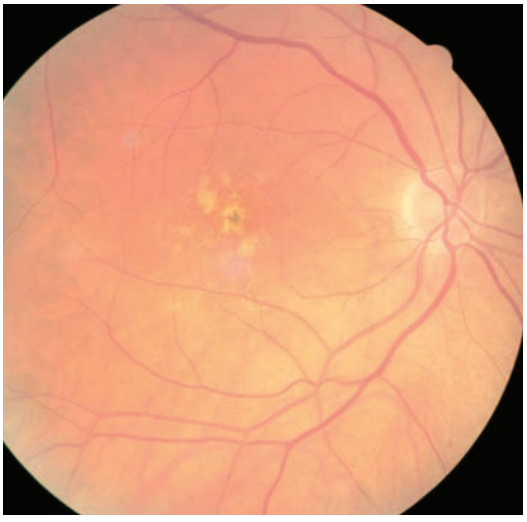

Photo: Julie Poteet, OD

This patient with intermediate AMD is at risk for progression and is a viable candidate for dietary supplementation use to increase carotenoid levels.

VITAMIN A

This vital substance supports all five senses, with particular relevance to olfaction, hearing and night vision. Three dietary forms exist: the preformed molecules retinol and retinyl ester, plus carotenoid (e.g., beta carotene) precursors to vitamin A. All forms of vitamin A are solubilized in the intestinal lumen and absorbed by duodenal mucosal cells.

In the retina, vitamin A is converted to retinol, oxidized to retinal and then to retinoic acid. Given its importance to ocular health, vitamin A was included in both the Age-Related Eye Disease Study (AREDS) and AREDS2 supplements.

However, the Blue Mountains Eye study found that elevated beta carotene intake was associated with an increased risk of AMD.[2]

B VITAMINS

This entire family can provide significant benefits and should be prescribed ideally within a comprehensive high-potency, multivitamin-mineral supplement. Here is a quick look at all eight members of the family:

Vitamin B1 (thiamin). This is part of the pyruvate dehydroxynase system responsible for converting carbohydrates into glucose, as well as breaking down fats and proteins. It helps produce the neurotransmitter acetylcholine, stimulates the production of red blood cells and relieves the effects of alcoholic cirrhosis, infections and hyperthyroidism. Thiamin protects nerves, preventing the degeneration of myelin sheath coverings that manifests as neuropathy in patients suffering from alcohol and/or uncontrolled diabetes.

This energy-producing vitamin is dramatically reduced in our American diet high in refined sugars, alcohol, coffee, tea and drugs that block its absorption. Benfo-thiamine, fat-soluble thiamin, is an excellent supplement for our patients suffering from neuropathy, cardiomyopathy and Alzheimer's disease.

Vitamin B2 (riboflavin). As part of the cellular electron transport chain, riboflavin is another B vitamin necessary for energy production. It helps convert carbohydrates to sugar, processes amino acids and fats, and fuels myriad cellular functions. Riboflavin is also a cofactor for GSH reductase—a major intracellular antioxidant.

Though riboflavin is a retinal photosensitizer in high doses, more common ocular deficiency symptoms are non-specific and subtle, such as conjunctival injection, photosensitivity and dry eye.

Vitamin B3 (niacin). This aids in digestive system function—converting proteins, fats and carbs into energy—supports properly functioning muscles and nerves, and promotes a 'glow' to the skin.

Those who are deficient (e.g., patients with pellagra disease) have weak muscles, digestive problems and skin irritation. In high doses, niacin has been used to treat schizophrenia.

Niacin comes in three forms, with different properties:

- *Nicotinic acid* reduces high blood LDL cholesterol.
- *Inositol hexaphosphate* (IP6) is useful against cardiovascular disease and lowering blood pressure.
- *Niacinamide* boosts mitochondrial function (and hence energy) that is reduced in aging and neurodegenerative diseases such as Alzheimer's and Parkinson's.

Vitamin B5 (pantothenic acid). This vitamin aids in producing neurotransmitters and steroids, enhances immunity and liver detoxification and assists in the extraction of fats, proteins and other vital nutrients from food.

The most common and irritating symptoms of vitamin B5 deficiency are burning foot syndrome, in which a person experiences a lack of feeling in their feet, accompanied by intense inflammatory pain, chronic fatigue and weakness.

Protein's Partner

Vitamin K, a group of fat-soluble vitamins, is a coenzyme for vitamin K–dependent carboxylase, which is required for the synthesis of proteins involved in hemostasis and bone metabolism.[1] Phylloquinone (vitamin K1) and menaquinones (MKs or vitamin K2) are naturally occurring forms of the vitamin, and it can also be found in supplement form.[1,2]

Vitamin K deficiency is linked to an increased risk of excessive hemorrhage. Research suggests women should have 90µg/day while men need 120µg/day.[2]

New research suggests that vitamin K could play a significant role in eye health, considering its link with the active matrix Gla protein (MGP), which is an inhibitor of calcification in arteries.[3]

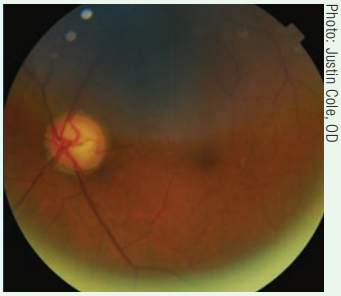

Photo: Justin Cole, OD

Vitamin K supplementation may have a protective effect against optic nerve thinning in glauoma.

With 11 years of follow up, researchers found a correlation between higher levels of MGP and healthier microvascular structure in the eyes, supporting overall eye health.[3]

According to the authors, this study highlights "the possibility that vitamin K supplementation might promote ocular health. Further studies should clarify the underlying molecular pathways and substantiate the speculation that vitamin K supplementation might promote ocular health and prevent glaucoma-induced optic nerve damage."[3]

1. NIH Office of Dietary Supplements. Vitamin K. https://ods.od.nih.gov/factsheets/vitaminK-HealthProfessional/. Accessed September 4, 2019.
2. Vitamin K. Micronutrient Information Center, Linus Pauling Institute, Oregon State University. https://lpi.oregonstate.edu/mic/vitamins/vitamin-K. Accessed September 4, 2019.
3. Wei F, Huang Q, Zhang Z, et al. Inactive matrix Gla protein is a novel circulating biomarker predicting retinal arteriolar narrowing in humans. Sci Rep. 2018;8:15088.

Vitamin B6 (pyridoxamine). This is a functional cofactor in a number of enzymatic systems involving proteins. The close association between pyridoxamine and enzymes assists in proper functioning of the nervous system. Deficiencies can affect cognition, ambulation, carpel tunnel, multiple sclerosis, immunity (lessening arthritis) and dermatologic issues of the skin and hair.

Vitamin B7 (biotin). A catalyst for controlling a number of metabolic reactions that provide energy from fats, proteins and carbohydrates, biotin is an essential component for maintaining skin, nail and hair health. Patients experiencing dry scalp, dandruff or hair loss might be suffering from biotin deficiency.

Vitamin B9 (folate). The natural form of B9 is essential for DNA creation, preventing mutations and the growth of new cells. Specifically, folate plays a role in building new red blood cells and stimulating peripheral end organ blood flow. This means that organ systems, including the eyes and brain, are well-oxygenated and working at full capacity.

The health benefits of vitamin B9 include prevention of heart disorders, stroke, cancer and neural tube defects during early pregnancy. Folate also helps provide relief from mental and emotional disorders.

Folic acid, the synthetic version of vitamin B9, has historically been used as a supplement. US grain products and some manufactured foods are fortified with it. Food folate (i.e., green leafy vegetables) or 5-methyltetrahydrofolate (5-MTHF) is far superior as it's absorbed and metabolized in the digestive system, avoiding any undesirable partially metabolized or non-metabolized folic acid.

The folic acid found in most supplements is not metabolized in the digestive system; rather, it moves to the liver, where multiple enzymatic reactions generate an active form, often resulting in high undesirable levels of non-metabolized serum folic acid and serum homocysteine.

Studies show that unmetabolized folic acid may have undesirable effects on the body, such as an increased cancer risk, masking of B12 deficiency or accelerated cardiovascular and ophthalmic vascular disease. Where possible, choose supplements with food folate or preformed 5-MTHF.

Vitamin B12 (cobalamin). This is cleaved from protein during digestion and is dependent upon gastric intrinsic factor and parietal cell hydrochloric acid. As with food folate, cobalamin assists in cell maintenance, particularly red blood cells, and DNA formation. Vitamin B12 provides relief for patients with pernicious anemia, megaloblastic anemia and sickle cell anemia, and supplementation often resolves symptoms of fatigue and neuritis (e.g., tingling, numbness), even when blood levels are adequate

Vitamin B12 deficiency is rampant in Americans for several reasons: (1) hydrochloric acid secretion diminishes as we age (achlorhydria); (2) from chronic over-use of proton-pump inhibitors to treat acid reflux disease; (3) by many individuals experiencing subclinical *H. pylori* infection, which interferes with healthy functioning acid secreting parietal cells; and (4) from the use of the diabetes drug metformin in some individuals.

VITAMIN C

This is the major extracellular antioxidant that sets the redox potential of cells. It is found at 10x to 30x serum concentration in every ocular tissue and protects blood vessels. It assists collagen formation, wound healing (including that of the cornea and retina), neurotransmitter synthesis, drug detoxification and more.

Deficiency results in slow healing, frequent infections, low platelets (typical of the elderly), bleeding gums, loose teeth, retinal microaneurysms and cataracts. Vitamin C reduces dermal bruising and thinning skin, important to those on blood thinners.

Virtually no one except supplement users maintain adequate vitamin C levels due to rapid excretion of this water-soluble vitamin. Maintaining a therapeutic dose for optimal blood concentration requires the synergism of polyphenols, serial dosing (i.e., grazing on plant food) or supplementation with liposomal C.

See, "The Virtues of Vitamin C," p. 14, for a detailed discussion of this important antioxidant's role in ocular health.

VITAMIN D

Some would argue vitamin D is a hormone. Vitamin D modulates the absorption of calcium and phosphorous from the small intestine, as well as more than 1,000 genes. It plays a seminal role in the top three killers: cancer, cardiovascular disease and Alzheimer's.

There are two forms: vitamin D2 (the less potent, plant-based ergo-calciferol) and vitamin D3 (i.e., fish liver cholcalcefirol). Vitamin D3 converts into 1,25-hydroxy-cholcalciferol, the most potent endogenous steroid hormone. The most abundant source of vitamin D is sunlight.

Optometrists should aim for a vitamin D status between 50ng/ml and 80ng/ml in our patients by calculating the required dose of D3 based on lab results. (Remember, 1,25-hydroxy-cholcalciferol serum liver reserve status varies by ethnicity, which is why it is critical to do this lab test to calculate the proper dose.)

While vital for everyone, optimal vitamin D levels are crucial for patients facing recalcitrant uveitis/retinitis, multiple sclerosis, herpes simplex and zoster reactivation, decreasing neovascularization in macular degeneration and patients with or at risk for diabetes and multiple systemic cancers.

Vitamin D repletion typically decreases excessive anti-VEGF treatments in housebound elderly patients. Vitamin D status also plays a role in lowering systolic blood pressure and the degree of arteriolar sclerotic retinopathy, arcus senilis and cardiovascular plaque.

Some 73% of Americans are insufficient or deficient in vitamin D. Its status is lower in those with higher melanin counts (i.e., darker skin) due to the pigment's interference with sun absorption. Vitamin D deficiency

is also common in older people, those living in northern latitudes and patients prescribed chronic use of proton-pump inhibitors.

VITAMIN E ISOMERS

This nutrient is composed of eight isomers: four tocopherols and four tocotrienols (alpha, beta, gamma, delta). Only one isomer of vitamin E (alpha tocopherol) was employed in the AREDS and AREDS2 studies, an obvious criticism.

Vitamin E tocotrienols are potent antioxidants in competition with the tocopherols. The best sources of gamma and delta tocotrienol (ideal for protection against cardiovascular disease, cancer and diabetes) derive from annatto beans. Tocotrienols increase tear production, retard cataract formation and reduce propensity for diabetic retinopathy and angiogenesis.

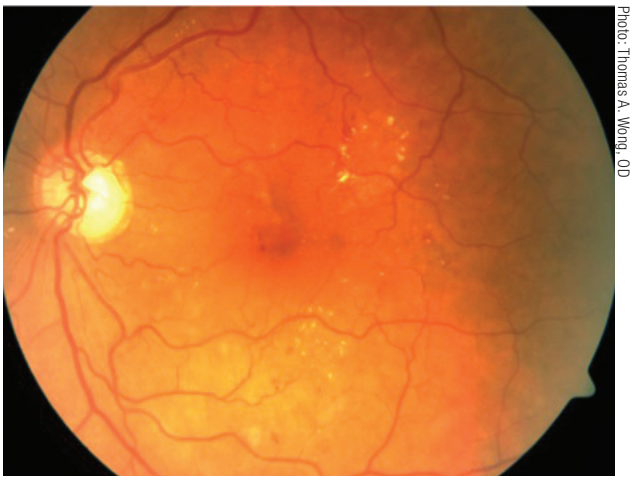

Photo: Thomas A. Wong, OD

The tocotrienol isomers of vitamin E have antioxidant effects that can lower a patient's risk of diabetic retinopathy and angiogenesis.

ESSENTIAL MINERALS

In contrast to vitamins, which are large molecules, minerals are atoms and ions—right off the periodic chart. Your body cannot make these; fortunately, the earth is a one-stop shop for everything your cells need. However, there has been a decline in soil nutrient levels within the last 50 years, with only a few minerals artificially re-introduced into the soil.

Calcium is key for muscle, heart and digestive cell messaging systems and is a constituent of bones and teeth. Adequate levels also support blood clotting, but calcium can be problematic when supplemented in excess (especially without balanced magnesium), where it accumulates in blood vessels, the mitral valve and soft tissue.

Chloride is a systemic electrolyte that maintains fluid and electrolyte balance, which is needed for production of hydrochloric acid for digestion.

Chromium is associated with insulin function and is required for the release of energy from glucose. Along with vitamin B3, its absence in the diet results in insulin resistance.

Copper is necessary for the absorption and use of iron, supports formation of hemoglobin and several enzymes, and is a cofactor of many enzymes, including cytochrome C oxidase. Labile copper is a strong divalent oxidizing mineral modulated by the concentration of binding liver ceruloplasmin as well as zinc status. In Wilson's disease, pathognomonic corneal deposits are found.

Excess copper is common in the US population due to the ubiquity of copper plumbing, use of unfiltered tap water, low ceruloplasmin from subclinical liver disease and lack of dietary zinc. Thus, high-quality adult multivitamin-mineral formulas do not contain copper. For those who need it, almonds are a great dietary source. AMD eyes and Alzheimer's brains are over-mineralized with this divalent mineral.

Iodine is a component of thyroid hormones and helps regulate growth, development and metabolic rate. Dietary deficiency is the result of fluoridated water in two-thirds of US jurisdictions, brominated US wheat products (i.e., dough fortified with potassium bromate) and unfiltered chlorinated water.

Iron, a divalent metal, is part of the protein hemoglobin molecule that carries oxygen throughout the body. Different intake requirements are based on age (younger: important for growth) and gender (premenopausal: important due to blood loss).

Iron is typically not included in high-quality adult multivitamins, as in excess it rapidly accelerates cardiovascular disease and oculovascular disease. While one-third of the US population has non-alcoholic fatty liver disease and excess stored iron, other patients have anemia of chronic inflammation, infection and malignancy where the body sequesters free and reactive oxidizing iron. AMD eyes are over-mineralized with divalent iron.

Magnesium (MG) is the center atom of chlorophyll in dark green leafy vegetables and is the fourth most abundant mineral in the body. MG is involved in more than 300 biochemical reactions and supports bone mineralization, protein building, muscular contraction, nerve impulse transmission, immunity and mitochondrial adenosine triphosphate energy production. This mineral is deficient, due to modern soil depletion and lack of intake of leafy vegetables in the American diet. In the past few decades, MG intake has dropped by 50% while the need

for magnesium has increased by 50%.

Magnesium protects against cardiovascular disease and diabetes and, along with potassium, naturally regulates blood pressure. An overly acidic first morning urine pH reflects a poor magnesium (and potassium) status.

It is important to encourage supplementation or weekly Epsom salt baths/footbaths in addition to a multivitamin for those taking a calcium supplement and those with MG lab values at 50% of 'normal' or below. Magnesium deficiency has been linked to retinopathy, neuropathy, foot ulcerations, acephalic migraines, twitching eyelids (ocular myokymia), cold fingers (Raynaud's phenomenon) and low-tension glaucoma.

Manganese, a cofactor for superoxide dismutase, is the principal antioxidant enzyme in mitochondria. Several enzymes activated by manganese contribute to the metabolism of carbohydrates, amino acids and cholesterol.

Molybdenum is a cofactor for the oxidases xanthine, aldehyde and sulfite, all of which facilitate cellular processes. A low molybdenum level is why some individuals are sensitive to sulfites in food and wine.

Phosphorus is required for the formation of cells, bones and teeth, and it maintains acid-base balance, digestion detoxification and sex drive. A phosphorous deficiency can lead to weak muscles, joints and bones as well as low stamina and even cognitive dysfunction.

Potassium maintains fluid and electrolyte balance, cell integrity, muscle contraction and nerve impulse transmission. Patients with kidney disease should avoid over-supplementation from food (e.g., vegetable juice, bananas). High serum potassium is a mortality risk, as it can stop the heart.

Selenium is a cofactor essential to the activity of antioxidant enzymes like glutathione peroxidase and works with vitamin E to protect cells from oxidation. It also helps protect patients against cancer and AMD, and converts T4 to biologically active T3 within the thyroid gland. Selenium is found in Brazil nuts and sulfur-rich foods such as garlic. It inhibits viral replication. Higher doses (e.g., 200mcg seleno-methionine) can typically be found in high-quality vitamins.

Sodium maintains fluid and electrolyte balance, and supports muscle contraction and nerve impulse transmissions. Along with chloride, it is needed for production of hydrochloric acid.

Zinc is a cofactor of many enzymes and a transporter of vitamin A. It is involved in the production of genetic material, proteins, sperm, immune factors and fetal development. It's also necessary for taste perception, smell and wound healing. In the eye, zinc is most concentrated in the retinal pigment epithelium, but also found in most other ocular tissues.

SUPPLEMENTS

Even those who pride themselves on regularly eating healthy may not be getting optimal amounts of certain vitamins and nutrients. Certainly, increasing environmental toxins and blue light exposure aren't helping.

As a result, we should all supplement our daily food intake with specific vitamins and nutrients. Specific to eye care, ocular supplements can help safeguard against progressive damage from age-related diseases such as AMD and cataracts, and preserve and enhance vision and all-around health. Eye care providers most often recommend AREDS supplements for ocular health, although both formulations are accompanied by controversy (see "Two Big Controversies in Ocular Nutrition," p. 41).

AREDS & AREDS2

These two trials, sponsored by the National Eye Institute (NEI), show benefits to using certain supplements to slow the effects of AMD.

Participants in AREDS were given one of four treatments: (1) zinc alone, (2) antioxidants alone, (3) a combination of antioxidants and zinc, or (4) placebo. Researchers evaluated supplementation of vitamin C (500mg), vitamin E (400IU), beta-carotene (15mg), zinc in the form of zinc oxide (80mg) and copper as cupric oxide (2mg).

The researchers concluded that individuals at high risk of progressing to advanced AMD stages reduced their risk by about 25% when treated with a high-dose combination of vitamin C, vitamin E, beta-carotene and zinc.[5] Within the high-risk group, the supplements reduced the risk of vision loss by about 19%.

For study participants who had no or early AMD, the supplements didn't provide an apparent benefit. They also had no significant effect on the development or progression of cataracts. High-dose zinc, however, was associated with elevated risk of genitourinary disease and beta-carotene with lung cancer risk in smokers.

AREDS2, a five-year study, was designed to test whether the original AREDS formulation could be improved by adding omega-3 fatty acids, lutein and zeaxanthin, removing beta-carotene and reducing zinc.[6,7] Researchers chose to add the new carotenoids in hopes of forestalling the risk of lung cancer found in the original AREDS for smokers. The study also examined how different combinations of the supplements performed.

Participants took one of four AREDS formulations daily for five years: the original AREDS formula, AREDS with no beta-carotene, AREDS with low zinc (25mg), or AREDS with no beta-carotene and low zinc. All participants also took one of four additional supplements or

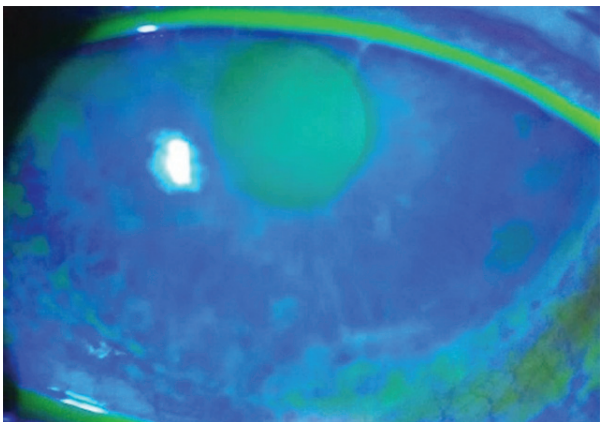

Photo: Nandra Mickles, OD, MS

Ocular surface staining in dry eye is a common target of omega-3 supplementation, but the recent DREAM study has challenged the practice.

combinations, including lutein/zeaxanthin (10mg/2mg), omega-3 fatty acids (1,000mg), lutein/zeaxanthin and omega-3 fatty acids, or placebo.

The study concluded that, though omega-3 fatty acids had no effect on the formulation, lutein and zeaxanthin appeared to be a safe and effective alternative to beta-carotene. Later, after further analysis, Emily Chew, MD, deputy director of the NEI Division of Epidemiology and Clinical Applications, noted that the study had also revealed that participants with low dietary intake of lutein and zeaxanthin at the start of the study who took an AREDS formulation with the carotenoids were about 25% less likely to develop advanced AMD compared with participants with similar dietary intake who didn't.[8]

In addition, Dr. Chew said that long-term use of AREDS supplements appeared to be safe and protective against advanced AMD.[8] While zinc was an important component of the AREDS formulation, she said, based on evidence from AREDS2 it was unclear how much zinc was necessary.

There is now an entire body of literature supporting the use of carotenoids for enhanced vision and cognitive function. (For more, see "Carotenoids: Front to Back Ocular Protection," page 21.)

OMEGA-3s

Numerous studies over the years have touted the ocular health benefits of omega-3 supplementation, and many eye care professionals have noted positive outcomes with the supplement for their patients. Still, the DREAM study, published in the May 2018 *New England Journal of Medicine*, found little or no evidence of a clinically meaningful effect of 3,000mg of a triglyceride-based fish oil for dry eye disease patients compared with a placebo group taking olive oil.[9]

In a multicenter trial, 535 patients with moderate to severe dry eye disease were randomized to receive a daily oral dose of either 3,000mg of fish-derived n-3 eicosapentaenoic and docosahexaenoic acids or an olive oil placebo.

After one year of supplementation, the mean Ocular Surface Disease Index score change was not significantly different between the omega-3 group (13.9 point reduction) and placebo (12.5 point reduction). There was also no significant difference in conjunctival staining score, corneal staining score, tear break-up time and Schirmer's test score between the groups.

The findings of the DREAM study initially caused quite a buzz in the optometric and ophthalmic communities, with some critics taking issue with the methodology of the study while others supported the validity of the study. Many vowed to keep using omega-3 supplementation due to conflicting research and their own positive clinical experiences, the preponderance of scientific evidence and its broad importance as a positive biomarker in human health.

THE ROLE OF THE OD

As with all new and potentially important research findings, it's up to individual practitioners to review the results, investigate the details of the study and consider their possible limitations, then make educated decisions on how to proceed as clinicians.

Eye care providers need to quiet the noise around them and do what they do best: help heal patients and teach them sustainable ways to prevent disease from taking root in their bodies. Our patients' eyesight and health are worth it. ❍

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The Virtues of Vitamin C

This substance is critical to eye health and function. Here's why it should be an important part of your arsenal.

BY THOMAS E. LEVY, MD, JD

Increased oxidative stress in and around the eye, as well as elsewhere in the body, is the most consistently identifiable evidence of any ongoing disease process. Antioxidants, and vitamin C in particular, can be a crucial addition to anyone's nutritional health to stave off such oxidative stress and the subsequent disease processes. For eye health specifically, vitamin C deficiency is characteristic of many common eye disorders.

Maintaining a higher intake of vitamin C reduces the incidence of ocular conditions such as cataract, glaucoma and age-related macular degeneration (AMD).[1-3] Prospective studies support the notion that increased vitamin C can also help slow disease progression and occasionally even reverse it, depending largely on the chronicity of the condition and the level of antioxidant supplementation.

Antioxidant molecules such as the carotenoids lutein, astaxanthin and zeaxanthin, along with vitamin E, are important in minimizing oxidative stress in the eye. While vitamin C is not mentioned nearly as often as a protective antioxidant in the eye as other antioxidants, it remains the pivotal antioxidant for minimizing ocular oxidative stress, since it is essential for keeping these other antioxidant molecules in the reduced, protective state.[4]

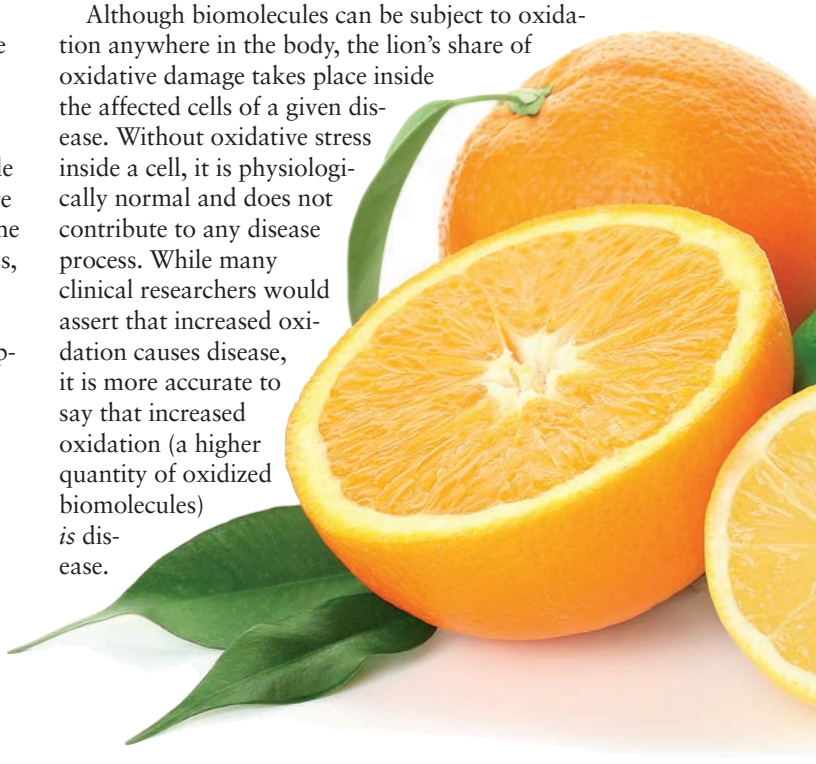
The soundest clinical approach is to keep the body supplied with a broad spectrum of antioxidant protection, with a special focus on high vitamin C blood levels.

An abundance of literature reaches the same conclusion: the greater your intake (whether dietary or supplemental) of vitamin C, the longer you live. Studies show that maintaining higher blood levels of vitamin C results in greater longevity, and the chance of death from any cause is clearly reduced.[5-14] This includes critically ill patients given intravenous vitamin C.[15]

DEFINING DISEASE

Biomolecules—such as proteins, sugars, enzymes, fats, nucleic acid—work best when they are in a chemically reduced state (having a full contingent of electrons). When they lose electrons to a pro-oxidant, they become oxidized and lose some or all of their normal functions and roles in metabolic pathways. Thus, all disease or tissue damage is secondary to the degree to which a given array of biomolecules have been oxidized.

Although biomolecules can be subject to oxidation anywhere in the body, the lion's share of oxidative damage takes place inside the affected cells of a given disease. Without oxidative stress inside a cell, it is physiologically normal and does not contribute to any disease process. While many clinical researchers would assert that increased oxidation causes disease, it is more accurate to say that increased oxidation (a higher quantity of oxidized biomolecules) *is* disease.



This means that the degree to which biomolecules are oxidized is the entire determining factor as to how advanced a disease or medical condition might be. Additionally, it directly determines the extent and degree of the symptoms that are present. It is also an important factor in determining the efficacy of any given therapeutic protocol.

All oxidizing agents are toxic, and all toxins are oxidizing agents in some fashion. Toxins cause their damage by oxidizing a unique variety and concentration of biomolecules based on the access afforded the toxin by its unique chemical structure.

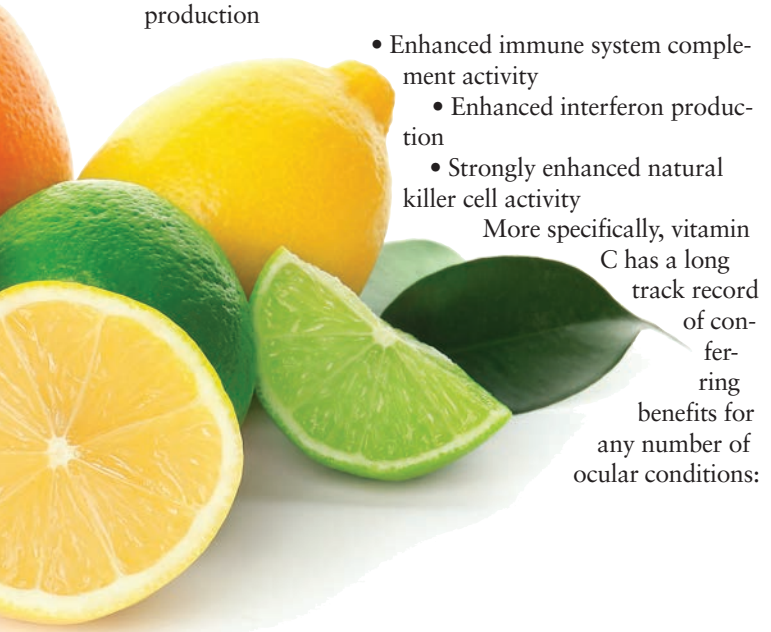
The only way to ameliorate, stabilize, reverse or even clinically cure a given condition is by restoring and maintaining enough oxidized biomolecules to a reduced, normal state with a sufficient influx of antioxidant molecules.[16]

SUCCESS BEGINS WITH C

Vitamin C, as the premier antioxidant in the body, is the primary supplier of the fuel—electrons—on which every cell in the body runs. Some of the characteristics that make it the body's most important antioxidant include its small molecular size; its similarity to glucose (allowing insulin to enhance intracellular uptake); its ability to penetrate all cells and tissues, including crossing the blood-brain barrier; its capability to donate two electrons per molecule rather than one; and its ability to regenerate other significant oxidized antioxidants. Additionally, vitamin C has an intermediate, stable form (ascorbyl radical) that can act as a buffer in a given microenvironment.

Vitamin C has also been documented to support the immune system in a number of different ways:[17-25]

- Enhanced phagocytic function of white blood cells
- Enhanced T lymphocyte response, proliferation and longevity
- Enhanced B lymphocyte proliferation and antibody production
- Enhanced immune system complement activity
- Enhanced interferon production
- Strongly enhanced natural killer cell activity



More specifically, vitamin C has a long track record of conferring benefits for any number of ocular conditions:

Retinal disease. The retina is one of the highest oxygen-consuming tissues in the body, with a metabolism that generates large amounts of reactive oxygen species (pro-oxidants).[26] As such, the retina is a tissue in need of substantial antioxidant protection to prevent or minimize the evolution of diseases related to oxidation-impaired function.[27]

In many ways, diabetes is the prototypical disease for demonstrating the negative health impact of increased intracellular oxidative stress (IOS). When vitamin C and magnesium levels sufficiently decline and calcium levels significantly rise inside cells, a metabolic state of elevated IOS always exists.

Part of the reason that intracellular levels of vitamin C are depleted in poorly controlled diabetes patients is that glucose and vitamin C directly compete with each for cellular uptake, as they are chemically similar molecules; the uptake of each is further facilitated by insulin, in contrast to passive uptake. The higher the blood glucose levels, the less vitamin C is able to enter the cells.[28,29]

In proliferative diabetic retinopathy, the degree of increased oxidative stress is massive. Such patients have a ten-fold decrease in vitamin C levels in the vitreous humor, and the degree of macular ischemia further correlates with the degree of vitamin C depletion.[30]

A study of 479 patients with nonproliferative diabetic retinopathy found that vitamin C given with statins resulted in a reduced complication rate.[31] In a secondary randomized study of these patients, researchers noted a stabilization of macular degeneration with improved visual acuity scores with regular supplementation of lutein, zeaxanthin and astaxanthin over a two-year period.[32]

Even in the absence of diabetes, this disease is related to increased oxidative stress, and research shows vitamin C significantly reduces the oxidative stress in human retinal pigment epithelial cells.[33] Supplemental antioxidants can be protective against AMD, and can significantly improve an array of visual function parameters in patients with AMD.[34,35]

In vitro, vitamin C has also demonstrated a dose-dependent effect in controlling the rate of cell replication in another retinal disease, proliferative vitreoretinopathy.[27]

Iatrogenic disease. Many toxins, often in the form of prescription medicines with toxic side effects, can cause oxidative damage to the retina and end up causing visual deterioration. As the most significant antioxidant in the body, vitamin C is the premier antitoxin. Acute poisonings unresponsive to all traditional measures will reliably be resolved by the acute administration of high amounts of vitamin C, as long as clinical deterioration is not too advanced.[37] No toxin has ever been shown to be refractory

Redox-Based Treatment Protocols

All effective treatment protocols strive to accomplish two goals: prevent or limit new oxidative damage to previously undamaged biomolecules, and repair (chemical reduction) biomolecules that have already been oxidized.

While these goals are straightforward and simple, reaching them can be difficult. Nevertheless, they are achievable. Basic treatment principles for all disease, regardless of the organ system or tissues involved, encompass the following objectives:

- Address new toxin exposures (dental and infectious, dietary, environmental, digestive)
- Neutralize (reduce) existing toxins already in the body
- Eliminate toxins in as non-toxic a fashion as possible
- Supplement (while completely avoiding calcium, iron and copper)
- Normalize critical hormone deficiencies (especially sex hormone, thyroid and cortisol)
- Minimize the use of prescription drugs (largely pro-oxidant in nature)

to the toxin-neutralizing capacity of properly dosed vitamin C. Any adequately dosed antioxidant can negate/neutralize a toxic presence if the chemical characteristics of the antioxidant permit sufficient access to the toxin—and vitamin C does it better than any other antioxidant.[38]

Glaucoma. Normal-tension glaucoma patients have lower serum levels of vitamin C than healthy controls.[39] In most cases of glaucoma, research shows a circulating vitamin C metabolite, O-methylascorbate can reduce intraocular pressure.[40] In a large meta-analysis, vitamin C and foods high in dietary antioxidants showed a protective effect against open-angle glaucoma, while other studies found greater glaucoma risk with lower vitamin C plasma levels.[41-43]

Cataracts. Vitamin C has been recognized as the most effective water-soluble antioxidant for reducing oxidative stress in the crystalline lens, and it can help protect the lens from damage due to ultraviolet light and radiofrequency exposure.[44,45] In senile cataract patients, vitamin C levels were lower compared with normal, healthy control patients.[46] Among patients with age-related cataracts, those with more advanced opacification had higher ratios of oxidized to reduced vitamin C.[47] Furthermore, oral vitamin C supplementation in cataract patients significantly increases the aqueous humor vitamin C levels, which can help combat the declining vitamin C levels researchers found in the aqueous humor surrounding the lens of aging patients undergoing intraocular lens implant survey.[48-50]

While vitamin C supplementation is an effective treatment for ocular conditions, delivery to the necessary ocular structures continues to pose problems.[51,52] Anecdotal reports indicate that eyedrops containing 1.25% glutathione, 1.25% vitamin C and 6.25% dimethyl sulfoxide, formulated by a compounding pharmacy and appropriately pH-balanced, have substantial positive impact for patients with the early stages of cataract formation. The dimethyl sulfoxide facilitates a high degree of tissue penetration by the glutathione and the vitamin C, the body's two most important antioxidants.

Corneal wounds. Several animal studies show vitamin C can accelerate corneal epithelial wound healing, enhance the genetic integrity of cultured corneal epithelial stem cells, and reduce neovascularization.[53,54]

Cryogels containing vitamin C and gelatin can support corneal healing while enhancing tissue matrix regeneration and maintaining transparency.[55] In patients with herpes simplex keratitis, both oral vitamin C and oral acyclovir were able to significantly reduce the risk of recurrent attacks.[56]

VITAMIN C IN PRACTICE

Because increased IOS is at the heart of so many chronic diseases, any agent that can bring oxidized biomolecules back to a normal, reduced state, has the potential to be a positive intervention. Although disease treatment protocols vary widely, the degree to which they prevent new oxidation while repairing old oxidation is the total determinant of how clinically effective they are.

Many antioxidants and nutrient molecules can reduce oxidized biomolecules; however, vitamin C is the most important agent for achieving this goal, largely due to its small size and ability to reach and penetrate all the cells of the body.

A diet that includes high amounts of vitamin C and other important antioxidants can go a long way to improving patients' overall health, but no diet can provide the same benefits that supplementation will provide.

Skeptics will cite studies that appear to show no benefit of vitamin C and other nutrients in combating disease. Consistently, such studies use incredibly low doses to support the claim that they are of no use for a given disease rather than acknowledging that it may be the low dose, not the supplement itself, that is of no apparent benefit.

For anyone still on the fence about vitamin C supplementation, rest assured that they are not prescription drugs and have little to no negative impact on the health, even with a high dosage. Given the amount of research now documenting their widespread benefits and nearly nonexistent toxicity, clinicians should have no fear in promoting their use to prevent or ameliorate disease. ❍

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Influencing Myopia: Science and Clinical Practice

In search of dietary and lifestyle changes that could alter the course of childhood refractive status and quality of life.

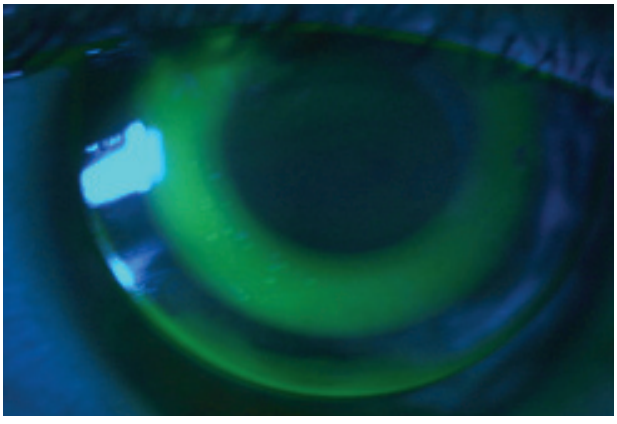
BY KARAN R. GREGG AGGARWALA, OD (NIH EQUIV), PhD, AND STUART P. RICHER, OD, PhD

Myopia is perhaps the most common diagnosis we optometrists encounter each and every day. Its prevalence is quite high in all age groups—estimated between 22% and 30% of the world population, and more than 50% in many industrialized countries—with significant progression in habitual computer users that extends over a decade beyond early adulthood.[1]

Because corrective lens wear is readily available and widely successful in counteracting myopic refractive error, clinicians may lack a sense of urgency about the need to intervene. But it is important to note that the burden of myopic macular degeneration and associated blindness is expected to increase significantly, fueled by a rise in myopia's global prevalence in children from 312 million in 2015 to 324 million in 2025.[2]

In short, myopia is more than just a refractive problem. It is an ocular health risk as well.

We at the OWNS are interested in a broad continuing dialogue concerning environmental factors involved in reducing the burden of myopia. More importantly, we wish to contribute to improved clinical practice.



Ortho-K lenses allow patients to enjoy correction-free vision until they reapply them at bedtime, as corneal reshaping occurs overnight.

INFLUENCE OF ACCOMMODATIVE LAG

Most busy practitioners likely haven't thought very deeply about the causes of myopia since optometry school, which may be expected as competing clinical responsibilities take precedence. Let's review the mechanisms of myopia so we might be better attuned to the modifiable risk factors within our reach.

Though it's a source of some debate, sustained hyperopic defocus is likely behind the etiology, onset and progression of myopia. Those espousing this view believe that a sustained lag of accommodation during continuous near work creates a chromatic signal encoded by retinal neurons and transformed into a neural endocrine signal for growth processes in the retina, choroid and sclera.[3,4] The optical stimuli at the retina that specify focus (e.g., comparison of luminance contrast between cone types enabled by longitudinal chromatic aberration) to control accommodation have also been demonstrated to drive eye growth mechanisms.[3-5]

Although the developing eye can attain emmetropia or compensate for lens-induced defocus without accommodation, the accuracy of accommodation is thought to be important for the process of emmetropization.[4] It is believed that the eye alters its growth to minimize

the time-averaged blurring of the retinal image, which depends upon refractive state, accuracy of accommodation and proportion of time spent at each viewing distance.[6,7]

Authors of a Singapore study on children ages seven to nine suggest an association of myopia with number of books read per week and lament that factors such as attention level or patterns of temporal interruption (e.g., brief periods of distance viewing) are important but rarely studied.[8] The study also noted the three-year change in axial length of the children at baseline was high and greater in those who were younger, females and those with a parental history of myopia.

Peripheral retinal cues can direct eye growth, with or without involvement of the foveal region in primates, but their role in humans has been difficult to demonstrate.[9-11]

Other important physiological variables that may contribute to the onset and progression of myopia include ciliary muscle fatigue, intraocular pressure, scleral distensibility and scleral remodeling.

AMBIENT LIGHT FACTORS

A recent study in rainbow trout demonstrated that ocular elongation is inhibited when the spectral composition of white light is dominated by short wavelength blue light or is lacking the red component.[12] An environment that deprives the eye of blue light stimulation—either from low color temperature tungsten bulbs, dim illumination, spectral filtering by spectacles or reduced sunlight exposure—will tend to make the eye vulnerable to myopia at low temporal flicker frequencies.[13]

Without blue light, the compensatory changes in choroidal thickness (moving the retina anteriorly) are insufficient to counter the associated elongation of the eye, and long wavelength light is known to induce a myopic shift. It is speculated that the myopia-inhibiting effect of blue light may be related to preferential stimulation of the 'ON' retinal pathway.

In closed environments, shifting the dominant wavelength of ambient white light to the short wavelength blue or violet region (360nm to 400nm) reduces ocular elongation.[14] Commercially available "cold white" LED bulbs (approximately 6500K color temperature, 7000 to 10,000 lumens) used at a distance of about two meters, may provide adequate yet safe levels of blue light.[13]

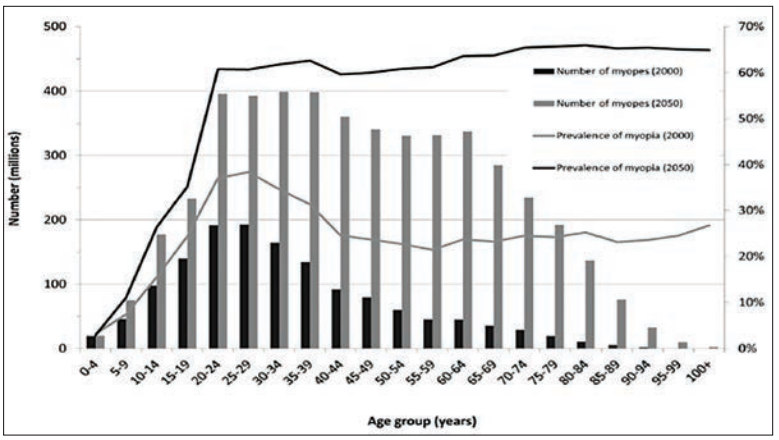
The effect of the short wavelength (i.e., near UV, violet and blue) component of white light on retarding the development of myopia is diminished if the light intensity is low. A wider spectral bandwidth of illumination induces wavelength-dependent defocus and improves the accuracy of dynamic accommodation. Integration of multiple visual cues from the retina plays a critical role in determining the direction of refractive change. Recent work also highlights the role of illumination (spectrum, intensity, temporal frequency), circadian rhythm disruption and light-induced changes in sex hormones.[15]

ENVIRONMENTAL FACTORS AND INTERVENTIONS

While genetics were once at the forefront of thought on why people develop myopia, this philosophy has shifted to include environmental factors, such as vitamin D levels and limited time spent outdoors.[16,17] Ethnic differences in myopia and the effects of parental myopia now seem likely to be explained, in part, by environmental influences.[16]

A 2007 study looked at whether parental history of myopia and children's outdoor activity levels could predict juvenile-onset myopia. Researchers found lower amounts of recreation and outdoor activity increased the odds of becoming myopic in children with two myopic parents—more than in children with either no or one myopic parent.[17]

Neural biomarkers of myopia have recently been identified, suggesting that high myopia is associated with abnormalities in several parts of the brain involved in visuomotor integration, the sensorimotor network and the limbic system.



The global prevalence of myopia has grown by 66% in the past three decades, and it has been estimated that nearly half of the world's population will be myopic by 2050.[1,2]

INFLUENCING MYOPIA: SCIENCE AND CLINICAL PRACTICE

Limiting time children spend using digital devices may remove one environmental impetus toward myopia development.

Efforts to control myopia typically involve the well-known muscarinic antagonists atropine and pirenzapine, but numerous other molecules and growth factors can play a role, including mediators of oxidative stress (e.g., free radicals and depletion of superoxide dismutase, glutathione) and vascular regulators such as nitric oxide. Increased ocular nitric oxide synthesis may be sufficient to prevent form-deprivation myopia and appears necessary for atropine-mediated myopia prevention.[18] A treatment modality based on nitric oxide would circumvent side effects of photophobia, glare, loss of accommodation and potential allergic side effects associated with atropine.

In a large sample study of six-year-old children from the Netherlands, researchers found lower serum vitamin D levels were associated with longer axial length, independent of outdoor exposure, and the association was similar for children of European and non-European descent.[19]

Limiting exposure to smart phones and head-mounted displays among children has become a staple of regimens to curb myopia. Reversed polarity of contrast on electronic displays may also be helpful.

Myopia research has also pointed to diet, including the intake of chromium, calcium, protein and sugar. An early investigation found people with myopic progression had abnormal hair concentrations of chromium and calcium and consumed excessive protein and sugar; a follow-up study confirmed differences in red blood cell chromium between high myopes and high hyperopes.[20,21] Evidence-based speculation suggests that development of myopia may be influenced by advanced glycation end-products that affect collagen elasticity and biochemical factors that regulate intraocular pressure and collagen synthesis. Ergonomic factors may be amenable to control by education in visual hygiene.[22] These variables require further exploration in their link to myopia, including the potential effects of an organic whole food diet rich in phytochemicals and nutrient-rich low glycemic index foods such as avocado.[23]

Clinically applied studies of physiology that may yield valuable insights include: enabling accommodation by vision therapy and nutrition; reducing vascular spasms in the ciliary body; improving cognitive function by dietary precursors to neurotransmitters; and regulating circadian rhythms.

To effectively influence the future prevalence of myopia, a concerted commitment of resources is required, as well as cooperation between professionals from various disciplines. ❍

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Carotenoids:
Front to Back Ocular Protection

Adding the marine newcomer, astaxanthin, to your plant food–based diet can fill in the ocular health gaps left by lutein and zeaxanthin.

BY STUART RICHER, OD, PhD, DOROTHY HITCHMOTH, OD, AND LISA RENZI-HAMMOND, PhD

Dietary lutein, zeaxanthin and mesozeaxanthin (an isomer of lutein) are important for maintaining a healthy retina. They aggregate in the macula more so than anywhere else in the body and compose the macular pigment (MP).[1,2] In the retina, they reduce the risk for age-related macular degeneration (AMD), as well as improve visual function.[3,4] The macular carotenoids protect photoreceptors and the retinal pigment epithelium (RPE) by serving as active antioxidants, absorbing short-wave light capable of damaging retinal tissue and by reducing inflammation.[5]

A less well-known carotenoid called astaxanthin, found in red algae, salmon and krill oil, complements plant-based carotenoids, supporting many functions the carotenoids don't (*Table 1*). While the three carotenoids help protect the retina and filter blue light, astaxanthin primarily supports the front of the eye and has been shown to have anti-tumor, anti-diabetic, anti-inflammatory and reactive oxygen species scavenging properties in humans. Animal models also show astaxanthin has protective effects on mitochondria and retinal ganglion cells.[6-9] Astaxanthin does not convert to vitamin A, so, unlike high doses of beta carotene, in this respect it is non-toxic if taken orally.[10] Human studies strongly support astaxanthin's consideration as a complementary dietary supplement.

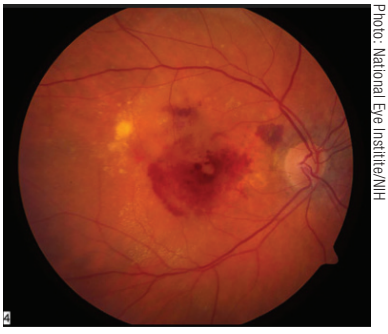


Photo: National Eye Institute/NIH

FIG. 1. Abundant evidence shows that AMD risk is elevated in patients deficient in lutein and zeaxanthin.

1st LINE OF DEFENSE: GREEN LEAFY VEGGIES AND FRUITS

Lutein, zeaxanthin and mesozeaxanthin are all antioxidants and free-radical scavengers that benefit the retina by filtering light before it reaches the photoreceptors and RPE, which staves off damage.[5] This is crucial for several disease processes and serves to enhance both visual and cognitive function:

AMD. Several studies have linked carotenoids with AMD risk (*Figure 1*).[3,11,12] Large cohort studies suggest that individuals with lower dietary levels of lutein and zeaxanthin are at increased risk for developing AMD.[11-13] Other studies suggest that higher MP optical density (MPOD), which represents longer-term lutein and zeaxanthin dietary intakes, is related to reduced risk for AMD.[14]

Building macular pigment is important. The Central Retinal Enrichment Supplementation Trial 2 found patients with non-advanced AMD who took antioxidant AREDS2 supplementation with or without mesozeaxanthin had significant increases in MP and improved contrast sensitivity.[15] AREDS2 suggests that antioxidant supplementation with lutein and zeaxanthin can reduce risk of progression to late-stage AMD.

Beyond prevention, research also suggests lutein and zeaxanthin may improve responses to standard treatments for wet AMD.

CAROTENOIDS: FRONT TO BACK OCULAR PROTECTION

A recent trial found oral supplementation with zeaxanthin in addition to triple therapy (photodynamic therapy plus intravitreal administration of bevacizumab and dexamethasone) led to improved visual function, with 27% of eyes gaining ≥15 letters compared with 9% in eyes treated with triple therapy alone. Adding oral zeaxanthin also led to a 74% reduced incidence of subsequent neovascular AMD in fellow eyes compared with eyes treated with triple therapy alone.[14] Supplementation may also lengthen the time between treatment cycles.[15]

REAR GUARD: SALMON AND KRILL OIL

Astaxanthin resides within krill and is what gives flamingos and salmon their distinct coloring. It's also found in shrimp, lobster and other orange-red marine life. In cells, it's mostly found in mitochondrial membranes, and has a unique chemical structure that allows it to fully span and protect cellular membranes with potent antioxidant and anti-inflammatory properties. It is believed to cross both the blood-retinal and blood-brain barriers.

Astaxanthin may help protect the RPE mitochondria, reduction of which is linked with AMD. The carotenoid may also ward off the increased mitochondrial DNA (mtDNA) lesions and reduced mtDNA repair capacity also associated with AMD.[16,17] Astaxanthin increases mitochondrial biogenesis and upregulates both the genes involved in energy production and cytochrome c, which is a component of the mitochondrial electron transport chain and a major PGC-1α-inducible protein.[18-20]

Astaxanthin is a considerably stronger antioxidant than zeaxanthin, canthaxanthin, lutein, B-carotene and alpha-tocopherol.[21] Such a protective role is crucial for several anterior segment conditions, including:

Pre-AMD Astaxanthin Pearls

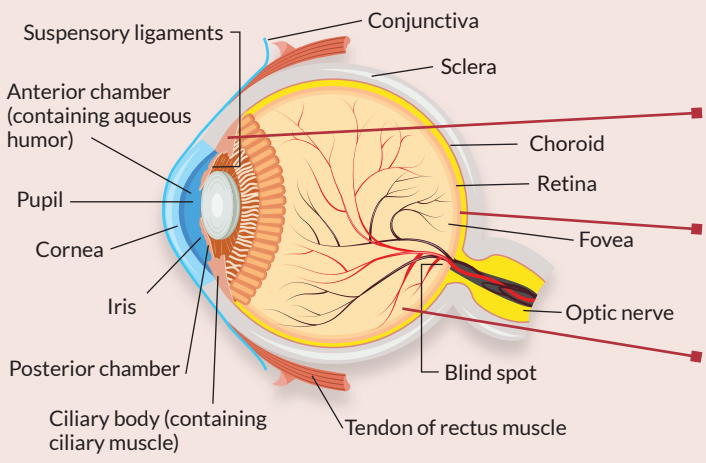
- Protects mitochondria from oxidative stress.
- Reduces UVB-induced oxidative stress.
- Promotes mitochondrial biogenesis.
- Promotes higher mitochondrial energy output.
- Protects lipids from oxidation.
- Promotes retinal blood flow.
- Provides anti-inflammatory properties (NFkB).

Accommodation and eye strain. Astaxanthin can help to improve accommodative speed, accommodative amplitude, near point of focus and depth perception *(Figure 2)*. These are all important to help focus and re-focus strained eyes, reduce eye fatigue and assist in visual recovery from screen time. One study shows a 21.7% increase in accommodative amplitude after four weeks of taking astaxanthin at 5mg/day.[22]

Astaxanthin also promotes circulation and nourishment of anterior and posterior segment eye tissue while alleviating oxidative stress. Specifically, astaxanthin increases ciliary muscle recovery and endurance, improves capillary blood flow and other rheology parameters and inhibits inflammation via the NF-kB pathway.

Dry eye. Astaxanthin plays a unique role in dry eye by providing antioxidant protection for the ocular surface and anti-inflammatory action to support lacrimation, reduce subjective symptoms and promote upregulation of ocular hydration aquaporin channels (*Figure 3*).

One study followed 22 patients between the ages of 45 and 65 who took astaxanthin 6mg/day and found those



Cause of Eye Fatigue	Astaxanthin
Ciliary muscle fatigue causes asthenopia or accommodation failure	Increases ciliary muscle recovery and endurance
Poor blood flow cannot support highly metabolically active organ	Improves capillary blood flow and blood rheology
Eye inflammation, e.g. visible swelling, sensations of heat and pain redness	Inhibits inflammation via NF-kB pathway

Source: AstaReal

FIG. 2. Potential mechanisms by which astaxanthin can help to improve accommodative and vascular function.

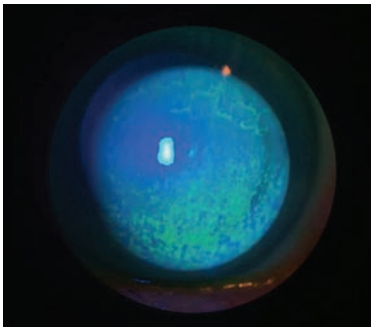


Photo: Cecelia Koetting, OD

FIG. 3. Dry eye patients may be able to achieve some symptomatic improvement with astaxantin use.

with dry eye disease experienced a 15% subjective improvement in lacrimation, 19% improvement in redness and 46% improvement in pain at one month.[23] The researchers note this is accomplished in part by increasing aquaporin 5 (water transporter) expression, which is important for tear production and saliva and pulmonary physiology.[24]

EYE HEALTH AND NUTRITION

The carotenoids are most often associated with AMD prevention but they have numerous other eye health benefits as well.

Cataracts. Carotenoids play an important role in defusing accumulated superoxide radicals in the lens and protecting against cataracts and post-op complications (*Figure 4*).[25] One study of 1,802 women found those who consumed high amounts of lutein and zeaxanthin were 32% less likely to have nuclear cataract compared with women who consumed low levels.[26]

Another study found preoperative cataract patients taking astaxanthin 6mg/day exhibited significantly lower aqueous flare intensity three days after surgery compared with controls, suggesting reduced post-surgical inflammation. They also observed increased superoxide scavenging activity and a decrease in total hydroperoxides in the aqueous of the cataract patients taking astaxanthin.[27]

Glaucoma. Because astaxanthin is localized to the ciliary body, it can increase the antioxidant capacity of aqueous humor, reduce pro-inflammatory factors in the trabecular meshwork and increase ocular blood flow.

In one study, 36 subjects took either astaxanthin 6mg/day or a placebo for one month, and the astaxanthin group's retinal capillary blood flow increased from 9% to 11%.[28] Another study used a higher dose of 12mg/day astaxanthin vs. placebo and found the astaxanthin group's blood flow velocity at the macula increased by an average of 15% in one month.[29]

Several animal studies show a reduction in the NF-KB mediated inflammatory response and reduced LPS-induced accumulation of protein, NO, TNF-α and PGE2, suggesting this carotenoid could play an importance role in uveitis as well as glaucoma.

Table 1. Complementary Dietary Carotenoid Functions[53]

Function	Astaxanthin	Lutein/ Zeaxanthin
Improve circulation	Yes	No
Improve accommodation/ focus	Yes	No
Reduce oxidative stress in aqueous humor	Yes	No
Reduce subjective symptoms of digital eye strain	Yes	Yes
Reduce subjective symptoms of dry eye	Yes	No
Reduce tear break-up time	Yes	No
Improve visual acuity	Yes	Yes
Help to reduce progression of dry AMD	No	Yes
Filter blue light	No	Yes
Improve contrast sensitivity	No	Yes
Improve glare tolerance	No	Yes
Improve MPOD	No	Yes

Visual function. Short-wave light is particularly prone to intraocular scatter, which can cause glare and reduce visibility.[26] A number of studies suggest that by absorbing short-wave light, MP can improve a number of visual functions. For example, higher MPOD is associated with reduced glare disability, reduced photostress recovery times, improved heterochromatic contrast sensitivity and improved temporal contrast sensitivity.[4,30-32]

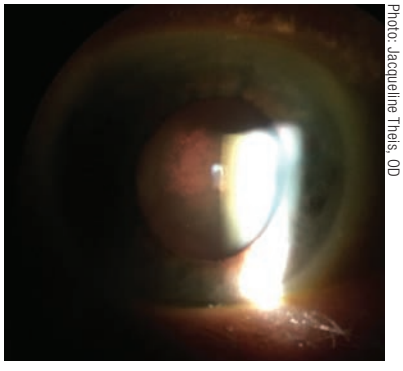


Photo: Jacqueline Theis, OD

FIG. 4. Studies show nuclear cataract development can be delayed by high intake of lutein and zeaxanthin.

BRAIN HEALTH AND NUTRITION

Increasingly, carotenoids are being recognized for their capacity to positively influence brain function.

CAROTENOIDS: FRONT TO BACK OCULAR PROTECTION

Cognition. Lutein and zeaxanthin are the dominant carotenoids in the neocortex of the brain.[33,34] Carotenoid concentrations in the brain often correlate with concentrations in the neural retina.[35] Since MPOD can be measured non-invasively, it may be possible to use MPOD as a biomarker of lutein and zeaxanthin in the rest of the cortex.[36]

A number of recent studies suggest lutein and zeaxanthin tend to be dominant in the cerebral cortex across the lifespan.[37] The brain seems to preferentially absorb lutein in particular, as concentrations in the cortex tend to be higher than dietary intakes would predict, even in infancy *(Figure 5)*.[37] Recent research suggests that binding proteins might be responsible for this selective uptake.[38]

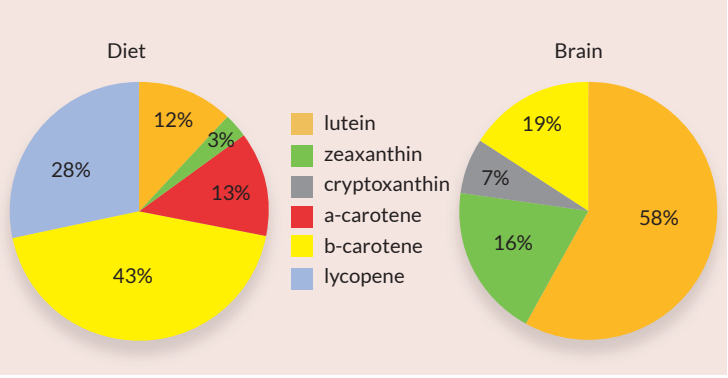


FIG. 5. Dietary intake vs. brain intake of carotenoids shows the brain's preferential absorption of lutein.[20]

The neural efficiency hypothesis predicts that lutein and zeaxanthin are capable of improving brain function by increasing processing speed, reducing neural noise and facilitating plasticity and white matter integrity—at any age.[39-44] This may be a possible mechanism to explain the finding that higher MP levels are related to improved cognitive function across the lifespan.[45-49] There is good evidence that astaxanthin is neuroprotective because of its positive effect on mitochondrial function and reactive oxygen species. Numerous articles demonstrate that this molecule protects against mechanisms implicated in Alzheimer's, Parkinson's, post-ischemic cerebral insult and amyotrophic lateral sclerosis.[50] Prescribing a diet rich in plant-based and marine carotenoids, or supplementing with these carotenoids, remains a largely untapped promising avenue of clinical practice and research.

Get To Know Your Colors

The vivid colors found in fruits, vegetables, flowers and marine life is at least in part because of the presence of carotenoids—pigments that enable many life-sustaining properties (e.g., photosynthesis) of these organisms. More than 1,100 carotenoids have been identified worldwide. They are categorized as xanthophylls and carotenes. The major carotenoids found in the diet are:

Xanthophylls (primarily yellow):

- Lutein
- Zeaxanthin
- Astaxanthin
- Beta-cryptoxanthin

Carotenes (primarily orange):

- Alpha-carotene
- Beta-carotene
- Lycopene

Depending on the country and culture, about 50 primary human dietary carotenoids are available and 20 are measurable in blood serum.

Lutein and zeaxanthin actively accumulate within the fovea at over 1,000-fold the concentration in the serum. Lutein, zeaxanthin and astaxanthin protect both the human lens and retina. Emerging research is identifying their potential role in protecting against skin cancer and cardiovascular disease, as well as in improving cognitive function.

GO ON THE OFFENSIVE

The sun, modern indoor LED lighting and digital screens all emit "bad blue" radiation. Such pervasive exposure requires a comprehensive protective approach that combines blue light filters—both internal (i.e., carotenoids) and external (glasses)—with avoidance of excess exposure:

- In recent years, ophthalmic lens and sunglass manufacturers have embraced blue light protection with new products that block deleterious wavelengths.
- Because the average American consumes less than 2mg of lutein and zeaxanthin per day, optometrists can play a crucial role in educating patients on the importance of increasing their dietary intake of colorful and dark leafy green vegetables, as well as salmon, for myriad health benefits. It is crucial to inquire if your patient regularly consumes dark green leafy vegetables (e.g., spinach, kale and collards) and salmon, shrimp or lobster. If not, encourage it. It is equally important that patients consume these carotenoids (or supplements) with fat. Females, anyone with higher body fat percentage and patients taking acid-blocking pharmaceuticals may require more.
- Augmenting our dietary intake of carotenoids with supplementation can add yet another layer of protection, particularly for at-risk patients. Patients at an increased risk

of AMD should consider both nutrition and supplementation with 4mg to 10mg of zeaxanthin and 6mg to 20mg of lutein. The exact amount needed for 'repigmentation' of the fovea will depend upon various patient characteristics such as gender, omega-3 index and baseline MPOD.[49,51] Research suggests 4mg to 6mg of astaxanthin—the amount found in 1.5 servings of sockeye salmon or three servings of Coho salmon—are important for eye health.

• Digital device manufacturers have been retooling their screens to minimize blue light emissions. And each of us has the most potent reducer of digital exposure always within reach: the "off switch."

Despite a dearth of clinical evidence, it seems prudent to prescribe blue light protection until the evidence accumulates otherwise. Children born in the last 10 years are exposed to direct blue light in ways that prior generations have not experienced. Precaution is prudent when it comes to protecting young patients in the context of the growing numbers of cases of AMD in younger patients.[52] ❍

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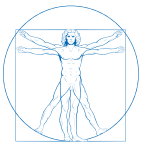


Uncover the Mechanisms of Macular Pigment

To determine a retina-friendly regimen for your patient, you need to see and track the work of the carotenoids in action.

BY PINAKIN GUNVANT DAVEY, OD, PhD

Of the numerous carotenoids found in nature and the 20 or so that can be detected in serum, just three—lutein, zeaxanthin and mesozeaxanthin—deposit in the retina, specifically the macula.[1,2] These three contain hydroxyl groups at the end of each molecule, which makes them biochemically distinct from the other carotenoids. The collective term for them is *xanthophylls*.[1,2] They give yellow coloration to the fovea.[3,4]

The density of the xanthophyll pigment in the retina potentially serves as a biomarker in healthy and disease states. Clinical measurement of macular pigment optical density (MPOD) helps the clinician steer the course of at-risk patients by revealing vulnerabilities that might warrant behavioral changes in food intake and augmenting by oral supplementation of various carotenoids.

Xanthophylls are at higher concentration at the center of the macula, in the axons of the photoreceptors and inner plexiform layers of the retina.[1,3,5] Their concentration decreases 100-fold when moved few millimeters to the periphery, where lutein is more prevalent than zeaxanthin 2.4:1.[1,6] This difference in concentration of both pigments correlates with the rod-cone ratio.[1,6] Mesozeaxanthin, believed to be a biochemical conversion of lutein, is a carotenoid present across the macula.[1,7,8]

Various factors influence MP levels, including the age of the patient, dietary intake and other health factors. This article explores the process of pigment deposition and how monitoring it can become a viable clinical tool to improve care.

FACTORS CONTRIBUTING TO MPOD

Macular carotenoids work to maintain the health of the retina, and thus visual performance.[3,4,9] With the exception of mesozeaxanthin, they are typically acquired through dietary intake of food such as vegetables, spinach, corn and egg yolks.[1,7,9] Certain dietary habits, like greater consumption of green leafy vegetables among the Chinese, yield a relatively higher dietary intake of lutein and zeaxanthin compared to individuals in the West.[10-12]

Several studies have investigated associations and correlations between MPOD and social factors such as sex, age, body mass index (BMI) and iris color. Although the findings are not overwhelmingly unanimous, males in specific age groups overall have higher MPOD than females.[13,14] The difference has been variously documented as being in the range of 13% to 38%, or perhaps none at all.[3] This finding could be due to the carotenoid-lipid transport system, which is hormonally controlled, as well as the influence of steroid hormones.[3,15]

There appears to be decline in MPOD values with increase in age, particularly in individuals 60 years and older.[13] There's also an inverse relationship between BMI and MPOD such that those individuals with higher BMI tend to have lower levels of MPOD.[13,16] This may in part be because carotenoids are stored in fat. An individual with higher body fat content may be storing more carotenoids in their body fat, and hence depriving their macula region of pigment. This could also serve as an explanation of why females have a lower MPOD level than males; women are known to have a higher percentage of

body fat.[3,15] BMI levels clearly also vary with dietary habits and thus may also explain the association between BMI and MPOD.[13,17]

DEVELOPMENTAL AND PROTECTIVE EFFECT OF CAROTENOIDS

The macular carotenoids may protect the retina—and especially the macula—by two proposed functions: (1) as a filter to blue light and (2) by decreasing oxidative stress. Blue light has short wavelengths, making it highly energetic; this in turn causes the production of excessive amounts of reactive oxygen species in the retina.[1] The macular pigment may decrease the amount of blue light reaching the photoreceptor cells as it has an absorption spectrum of 400nm to 450nm, making it ideally suited to serve as a blue-light filter.[1,9,18] Second, these pigments may be protecting the macula from oxidative stress by neutralizing reactive oxygen species, acting as antioxidants in the inner retina and photoreceptor retinal pigment epithelium (RPE) complex.[1,9,18]

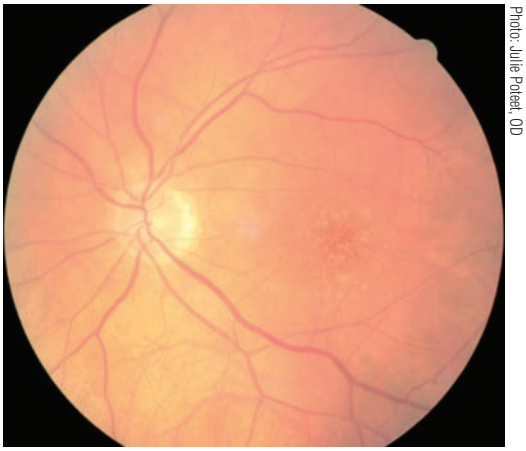


Photo: Julie Poteet, OD

This patient qualifies as intermediate AMD and is progressing to the advanced stage due to the pigment clumping centrally.

These macular pigment features have led researchers to think that high density levels could help protect individuals from developing eye diseases such as age-related macular degeneration (AMD).[9,18] Further, filtering blue light in elderly individuals with early AMD can enhance driving vision.[19]

There is early evidence that nutritional supplements may play a role in diabetic eye health, providing a clinically meaningful improvement in contrast sensitivity color vision without altering glycemic levels.[20] The carotenoids lutein and zeaxanthin are also deposited in the brain, and there is mounting evidence of its role in cognitive function. Histologically, it has been shown that the levels of lutein and zeaxanthin in the occipital cortex are correlated to their levels in the retina.[21] Further, these levels have been correlated with academic performance and cognitive function during developmental years as well as in an aging population.[22-24]

TECHNIQUES TO MEASURE MACULAR PIGMENT OPTICAL DENSITY

Given that the carotenoids levels can be augmented in an individual with oral supplementation, measurement of the levels of carotenoids is of importance in clinical care. It will be useful to obtain a measure of MPOD, which is repeatable and reliable. It may also have a role in monitoring changes and treatment efficacy.

To measure macular pigment levels clinically, we can use noninvasive techniques, which are categorized as *psychophysical* or *objective*.[4,9] The difference relies in that psychophysical techniques require participation from the subject, whereas objective techniques require minimal involvement from the subject.[4,9]

Heterochromatic flicker photometry (HFP). This psychophysical test has replaced most the other psychophysical techniques. Some advantages of HFP are relative ease of testing and its shorter measurement time.[4,9] The mode of action is based on the macular pigment's absorption spectrum at the retina, specifically the macula and fovea.[4,6,9]

HFP determines the MPOD by displaying two light stimuli of different wavelengths, which the patient perceives as a flicker.[6,9] The stimuli alternate between a blue light of short wavelength, which is maximally absorbed by the macular pigments, and a green-yellow light of longer wavelength, which the pigments do not absorb.[6,9]

The main advantages of heterochromatic flicker photometry are the ability to do the test through an undilated pupil, the device's relatively low cost, and the repeatability and validity of MPOD measurements generated.[4,6,9] However, in certain situations patients are not able to perceive the flickering light and this device is not suitable for the study of young children and/or people with poor visual acuity.[4,6,9] The test usually takes about five minutes, including patient education time, and only needs to be performed on one eye as it has excellent correlation to the fellow eye values.[25]

Motion photometry. Another psychophysical test, motion photometry is similar to HFP in that both techniques use two light sources with different wavelengths.[4,9,26] However, motion photometry uses the light stimuli to illuminate the bars of moving square wave gratings. The intensity of the light is adjusted until the moving square slows down or changes direction.[9,26] As in the HFP technique, the test is performed at foveal and parafoveal locations. The MPOD peak measurement is calculated by taking the log ratio of the differences in intensity between the stimuli perceived at fovea and parafovea.[9,26]

UNCOVER THE MECHANISMS OF MACULAR PIGMENT

Now, let's turn our attention to three objective techniques.

Fundus reflectometry. This measures MPOD on the basis of light reflected from the retina and the choroid.[9,27,28] It uses light of two wavelengths: one absorbed by the macular pigments (in the blue spectrum) and another that is not absorbed. The device performs two analyses. First, it compares the reflection of light at the central and peripheral regions.[9] The second method is based on spectral analysis, which involves analyzing the spectrum of the reflected light from a specific region of the retina.[4,9]

Unlike HFP, fundus reflectometry is an objective method of measurement and thus may obtain MPOD estimates in pediatric and special needs populations.[9] It has also proven to be repeatable, and estimates of MPOD can be obtained in short duration.[4,9,27,28]

Recently, a near-commercial prototype (ZeaVision) was evaluated in our lab and preliminary results of its repeatability and reproducibility were reported.[28] The major advantage of fundus reflectometry using a spectral analysis is that it can identify the individual levels of lutein and zeaxanthin in the retina, along with MPOD values and lens optical density. Our team also found the MPOD measurements more repeatable than the psychophysical technique and they can be obtained without dilation. However, if accurate measures of lutein and zeaxanthin are desired, pupillary dilation is preferred; precise alignment and signal strength from the retina may influence its values.

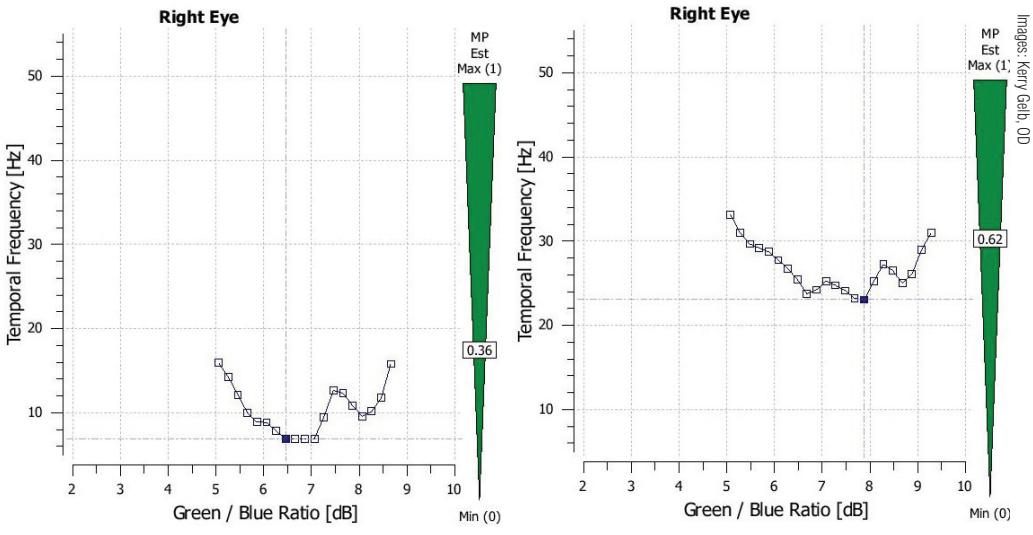
Fundus autofluorescence (FAF). This is another objective technique to measure MPOD *in vivo*. It is based on the intrinsic fluorescence or autofluroescence of lipofuscin, a waste product that accumulates with age on the RPE.[4,9,29] Lipofuscin is the main fluorophore in autofluroescence and will fluoresce when excited with light wavelengths between 400nm and 590nm. The absorption spectrum of lipofuscin is similar to that of the macular pigments (400nm to 540nm).[4,9,29]

Macular pigments are located in the axons of the photoreceptors and inner plexiform layers of the retina, which is anterior to the location of lipofuscin in the RPE. The lipofuscin fluorescence will be less pronounced in eyes with higher macular pigment density and greater in eyes with decreased macular pigmentation.[9] MPOD values are calculated by measuring the difference between autofluroescence emitted from the fovea and parafovea.[9,29] A recent report showed that fundus autofluorescence is strongly associated with macular pigment levels.[30]

Raman spectroscopy. This new technique is currently being developed for MPOD measurement and is not yet clinically available.[9] When a monochromatic light is directed through any molecule, it will result in two types of light scattering: elastic and inelastic.[9] The inelastic scattering causes a shift in the wavelength of the incident light, known as Raman shift, which is molecule-specific.[9,31] When the incident wavelength is similar to the absorption spectrum of the molecule, there is an enhancement of the Raman shift, thus allowing for the molecule to be identified.[9]

Raman spectroscopy can be used to identify macular pigments because these substances exhibit five orders of magnitude of resonance enhancement upon excitement by 488nm of argon laser light.[4,9]

This technique has gained interest from researchers, as it is the only technique that measures the pigments themselves instead of measuring pigments indirectly by analyzing other structures.[31] One of the main advantages of this



The QuantifEye MPOD measurement instrument shows MPOD improvement after supplementation with a daily carotenoid formula.

technique is that it is sensitive and specific for macular carotenoids and can be used in subjects with low visual acuity.[9,32] Some disadvantages are its need for pupillary dilation and the use of highly specialized and expensive devices.[9,32]

PHILOSOPHY OR PHYSIOLOGY?

We are what we eat, goes the saying. In an ideal world, our diet is our medicine and there will be no need for nutraceuticals to supplement or augment our poor diets. We live far from such an ideal, however, and the consumption and the role of nutraceuticals in managing chronic disease is indeed increasing. Just like the managing of diabetes patients without HbA1c measurement cannot be imagined, I am of the opinion that the use of xanthophyll supplements without baseline measurement of MPOD makes no sense.

There is significant evidence about the validity of the aforementioned multiple techniques to measure MPOD. Low levels have shown association with different disease states, and there is evidence that MPOD values can change with oral supplementation. However, due to the multifactorial nature of disease, the efficacy of carotenoid supplementation is still to be unequivocally proven. Further research is indeed needed to establish treatment regimens and protocols of carotenoid supplementation when and how to use MPOD values clinically to identify and monitor disease progression. However, we can be certain that the need to measure MPOD clinically is not in dispute. ❍

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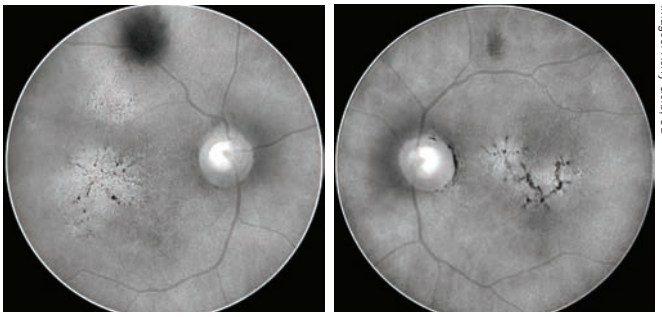
Conflict of Interest statement: Dr. Davey is a researcher and consultant for Optovue, ZeaVision and Guardion Health Sciences.



Images: Kerry Gelb, OD

FAF imaging can help reveal macular degeneration due to the accumulation of lipofuscin.

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Gut Instinct: Why the Microbiome Matters

It can be considered an additional human organ, rivaling the liver in the number of biochemical reactions in which it participates.

BY JULIE POTEET, OD, CNS

One cannot open a magazine these days—whether it be a scientific journal or *Newsweek*—without seeing something on the microbiome or probiotics. The hype surrounding the explosion of microbiome research, driven by Internet gurus and corporations aiming to make a profit, far exceeds the scientific validation of many of the claims. Although we are just at the tip of the iceberg in our understanding of the impact that our commensal microbes have on us, we now know some important details about how our lifetime partners, the trillions of bugs that live in and on us, affect us.

GO WITH YOUR GUT

Of all the parts of the microbiome—from the ocular to the oral—the gut microbiome is by far the most researched, and we know that it orchestrates human metabolism, immunity and gene expression. Researchers have also mapped out the role it plays in any number of systemic functions, including the production of certain B and K vitamins, neurotransmitters, and short-chain fatty acids important for brain health and in maintaining the integrity of the gut lining. The gastrointestinal (GI) microbiome also modulates the immune system by shifting T-helper cell balance towards Th1, resulting in decreased production of IgE and eosinophils, dampened hypersensitivity reactions and intestinal inflammation, greater oral tolerance and prevention of atopic diseases. It facilitates xenobiotic metabolism, important for the absorption and proper functioning of phytoestrogens, lignans, flavonoids and some medicinal herbs.

Most importantly, a healthy microbiome provides protection against colonization of the intestinal tract with potentially pathogenic bacteria afforded by the intestinal flora. A healthy microflora plays a vital role in weight maintenance and energy homeostasis, preventing obesity by its increased capacity to harvest energy from the diet.

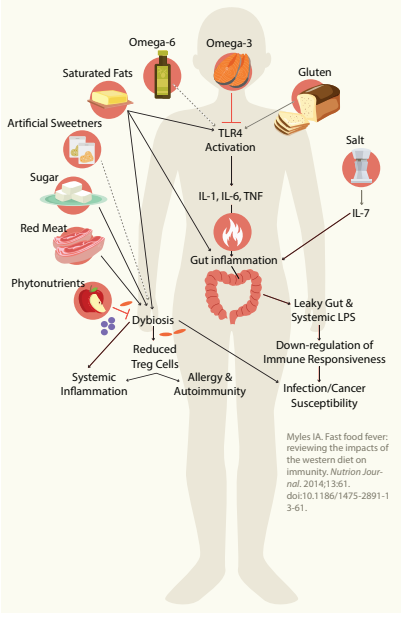

FIG. 1. In recent years, scientists have discovered that the gut microbiome orchestrates human metabolism, immunity and gene expression.

The foods we choose impact our microbiome and dictate the epigenetic expression of immune system function (*Figure 1*). Since almost every ocular disorder involves an inflammatory component, it is our duty to educate patients on proper nutrition because we must change the diet to change the microbes.

THE CONJUNCTIVAL MICROBIOTA

The microbial community of the ocular surface is more diverse than that of the skin but contains a significantly lower quantity than other bodily surfaces. This disparity is thought to be due to the antibacterial effect of tear film components.

In contact lens wearers, however, the ocular microflora is less diverse (more akin to that of the skin) and contains

Probiotic Myths Busted

Myth 1: Research conducted on one probiotic strain can be accurately extrapolated to other strains within the same species.

Truth: To assess the quality of the bacteria in a given supplement or probiotic food, you need to know not only the species of bacteria but also the strain because different probiotic strains have different actions. We use different strains of bacteria for different therapeutic applications. As an example, researchers compared two *Lactobacillus* strains in the treatment of viral gastroenteritis: *L. casei* subspecies *casei GG* (LGG) and *L. casei* supspecies *rhamnosus* (lactophilus).[1] The specific strain made a significant difference in the duration of diarrhea: 1.8 days in the LGG group compared with 2.8 days in the lactophilus group. On day two, only 19% of patients in the LGG group had diarrhea vs. 64% of subjects in the lactophilus group. The researchers also noted that rotavirus-specific IgA levels were significantly higher in the LGG group during the convalescent period, showing superior efficacy of one strain of *L. casei* over another.

This is important, as patients can waste time and money on probiotics not knowing the strain included in the product may not be effective for their condition. One study found strain 299v of *Lactobacillus plantarum* significantly decreased abdominal pain severity, frequency and bloating in patients with irritable bowel syndrome (IBS).[2] However, another study noted a similar strain, *Lactobacillus plantarum* MF1298, significantly worsened IBS symptoms—so much so that patients preferred the placebo.[3]

Myth 2: Don't use probiotics during antibiotic treatment, as antibiotics with kill all the probiotics.

Truth: Research shows that concurrent administration of probiotics with antibiotics not only significantly decreases antibiotic-related side effects, but also attenuates antibiotic-associated damage to the gut microbiota.[4] It is good clinical practice to prescribe over-the-counter *Lactobacillus rhamnosus GG*—a widely available probiotic and one of the most well-researched strains—concomitantly to prevent damage to the gut microbiome from antibiotic use.

Myth 3: Probiotics are best taken on an empty stomach.

Truth: Research clearly shows improved bacterial survival when probiotics are taken with a meal (preferably a larger meal such as dinner). Dairy-, fiber- or grain-based meals optimize survival through the upper GI tract.[5,6]

Myth 4: Probiotic strains ingested orally will permanently colonize the GI tract and you can re-colonize with probiotic supplements.

Truth: No exogenously supplied probiotic strain permanently colonizes the human GI tract. Once you stop taking a certain strain, it will eventually die off. You cannot re-colonize permanently by taking probiotic supplements for a limited time.

Myth 5: Infants should only be supplemented with strains of Bifidobacterium infantis.

Truth: Babies need special baby probiotics. By week one of age in vaginally-delivered, breastfed infants, the flora is dominated by *Bifidobacterium* spp. and *Ruminococcaceae* spp. but a multitude of other species are present as well.[7-9]

Myth 6: Giving probiotics in supplement form (i.e., capsule, powder or tablet) is superior to food forms (i.e., yogurt).

Truth: Yogurt often contains greater numbers of viable bacteria. In one study, researchers found 100 million bacteria provided in a dairy base led to a greater number of live bacteria in the colon than 10 billion provided in a capsule.[10] Numerous clinical trials show that medicinal yogurts have therapeutic effects such as decreased rates of vaginal candidiasis and decreased abdominal adiposity and body weight.[11,12]

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more gram-negative species. Researchers are still trying to find out if the increased risk of eye infections in contact lens wearers is related to lenses contaminated with bacteria from the finger or if lenses exert selective pressures on the eye's bacterial community in favor of skin bacteria.

Aside from acute ocular surface infections, the colonic microflora's influence on ocular health is, in general terms, far more important to ocular disease than the conjunctiva's due to the colonic microflora's ability to modulate the immune system and create inflammation and autoimmunity elsewhere in the body.

CONSEQUENCES OF DISRUPTION

Dysbiosis is the growth of potentially pathogenic microorganisms over their beneficial counterparts or alterations in the metabolic activities of the flora. Although different subtypes of dysbiosis exist based on location, research shows dysbiosis of the GI tract, where the majority of our microbiome microorganisms reside, has the greatest impact on immune system dysfunction and chronic and degenerative diseases.

Any number of outside forces can lead to a change in the intestinal flora:

Prescribing Pearls

Before recommending any probiotic supplement, make sure you know the strains it contains. Ensure these strains exhibit the desirable criteria (based on published research, not just the manufacturer's word). Avoid products that do not detail their strain(s). Choose the correct strain to treat the clinical scenario at hand, as each probiotic strain should be viewed as a unique therapeutic agent with specific actions and applications. Lastly, you cannot extrapolate research results from one strain to another, even if they are within the same species.

Antibiotics. Of all the factors that can impact the gut microflora, antibiotics have the greatest detrimental effect. Research using culturing techniques suggests quantitative changes could last up to 40 days after one round of antibiotics. Metabolic derangements can last up to 18 months. New research using more sensitive molecular analysis techniques (RNA studies) has revealed the presence of antibiotic-resistant microorganisms for up to four years post-treatment.[1,2]

Alterations can last significantly longer than previously believed: 18 to 24 months after the use of clindamycin and four years after triple therapy for *Helicobacter pylori*. Some organisms never recover.

Stress. This induces changes to the GI tract's motility and secretions. In addition, increases in the circulation of the stress hormone norepinephrine acts a growth inducer to potentially pathogenic members of the microflora.

Caesarean sections. Research suggests babies born via C-section have a different microbiome. One study found bifidobacteria was present in 56.6% of vaginally delivered infants at day three and in 0% of C-section infants.[3] This disturbance in the gut microbiome of C-section babies can last for at least six months.[4]

Birth location. Where a baby is born can also impact the microbiome. Research suggests full-term infants who were born vaginally at home and were breastfed exclusively have the highest numbers of bifidobacteria and the lowest numbers of *Clostridium difficile* and *Escherichia coli*—the most beneficial gut microbiota.[5]

Formula feeding. Babies fed formula are more often colonized by *E. coli*, *C. difficile* and *Bacteroidia fragilis* compared with exclusively breastfed infants.[5,6] Counts of these microorganisms are also significantly higher. There is also the presence of different bacterial species.

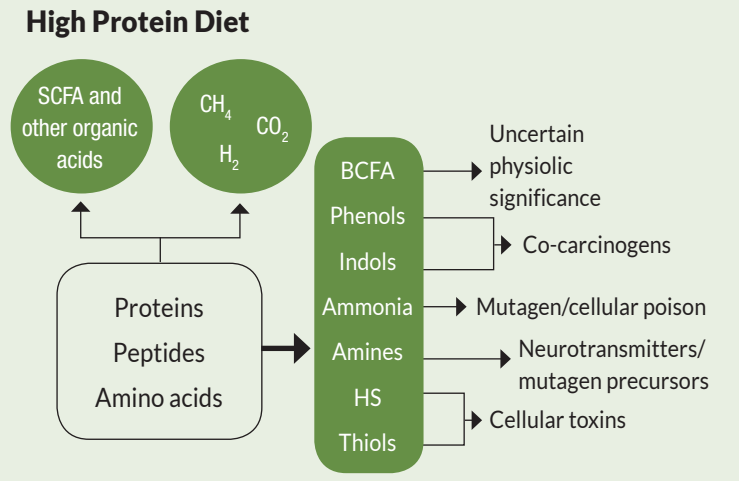
Diet. Sulphate and sulphite compounds are often added to foods (e.g., dried fruits and vegetables, shellfish, packaged fruit juices, baked goods, most junk foods, white bread and the majority of fermented alcoholic beverages) as preservatives. These cause the growth of sulphate-reducing bacteria, which increases hydrogen sulphide production and causes intestinal hyperpermeability and the inhibition of colonocyte metabolism.

High-protein diets can be particularly destructive to the GI microbiome. Protein is fermented by members of the microbiota (putrefaction), producing potentially harmful metabolites (*Figure 2*).

The more protein consumed, the more indoles, phenols, hydrogen sulphide and ammonia produced.[7,8] Phenol and indole production may be attenuated by an increased fiber intake, which decreases colonic pH due to short-chain fatty acid production.[7] The production and toxicity of colonic ammonia can be attenuated through prebiotic consumption.[9,10]

High-protein diets also induce changes to the ecosystem such as decreases in fecal concentrations of bifidobacteria—research shows a 50% decline on a high-protein, low-carb diet in just four weeks.[11] This dietary choice also decreases the concentrations of butyrate-producing species. All of these changes can be attenuated through prebiotic consumption.

High-fat diets are associated with increases in the ratio of gram-negative to gram-positive bacteria, which causes an increased proportion of lipopolysaccharide-containing microbiota in the gut and a greater pool of luminal endotoxin.[12] Meals high in fat increase endotoxin absorption wherein postprandial endotoxemia causes low-grade



Products of protein putrefaction in the colon (Macfarlane & Macfarlane, 2012)

FIG. 2. These diets can create a significant GI microbiome imbalance.

systemic inflammation.[13] The higher the fat content, the higher the serum level of endotoxins. Saturated fat appears to further enhance endotoxin absorption, while omega-3 fatty acids and concurrent consumption of 30g of fiber attenuate postprandial endotoxemia.[14,15]

Diets high in refined carbohydrates can disrupt the GI microbiome in the following ways:

- Slow intestinal transit time, increasing exposure to potentially toxic bowel contents
- Alter the colonic gas metabolism, which can lead to changes in the species composition of the flora
- Decrease short-chain fatty acid production
- Increase colonic pH

Diets low in fiber increase fermentation of the protective layer of mucin and peptides/proteins, due to the limitation in food sources (fiber/resistant starch), which compromises the mucosal defense and increases production of toxic putrefaction products. This causes direct contact between colonic cells and bacterial products and antigens, leading to inflammation and increased mucosal permeability.

Sucralose consumption, often in the form of artificial sweeteners, causes significant changes in the microflora, including reductions in beneficial bacteria such as bifidobacteria and lactobacilli and reductions in total anaerobes and aerobes. It also causes increased fecal pH.[16]

GETTING BACK ON TRACK

Prebiotics, probiotics, colonic foods and antimicrobials can all help combat dysbiosis. Prebiotics and probiotics can be consumed in supplement form and they are being added to commercial foods to promote a healthy digestive track. There are many different types of prebiotics and probiotics and they both work synergistically to promote the growth of beneficial flora.

Prebiotics are complex carbohydrates—oligosaccharides—that are not digestible. This means they can survive the rough journey through the digestive tract, making it safely into the colon. Prebiotics selectively stimulate the growth of beneficial microorganisms.

Xylooligosaccharides are a preferred form of oligosaccharide manufacturers often use because they can target good bacteria using a lower dosage than other prebiotics. In fact, doses as low as 1.5 to 2 grams can modify the gut microbiome significantly, resulting in an increase of good bacteria and a decrease of the bad.[19] Prebiotics include foods such as breast milk (infants), fruits and vegetables, tea, chocolate, fermented foods and those rich in polyphenols and vitamin D.

Probiotics are live, mostly gram-positive, bacteria (e.g., *Bifidobacteriaum*, *Lactobacillus*, *Lactococcus*, *Pediococcus* and other non-pathogenic strains of *E. coli*). These generally promote intestinal barrier integrity, prevent bacterial translocation in the gut and reduce inflammatory response.

Colonic foods serve as substrates for the endogenous colonic bacteria, thus indirectly providing the host with energy, metabolic substrates and essential micronutrients.[17] Examples of colonic foods include carrots, cocoa, green tea, brown rice and prebiotic foods such as onions, garlic, chicory root, barley, bananas, leeks and apples.

Fecal microbiota transplantation, also known as fecal bacteriotherapy or fecal infusion, an emerging method to treat dysbiosis, uses "the principle of engrafting the microbiota from healthy donors into a patient recipient to re-introduce or re-establish a stable environment that influences both the endogenous microbes and the host."[18]

Dysbiosis is implicated in eye and systemic disease associated with vision loss and other morbidity. Treatments that can help restore human microbiota homeostasis can be simple and have been shown to support improved outcomes. Optometrists should understand these treatments and prescribe them accordingly. ❍

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DIET

Put Wellness on the Menu

Learn how the right dietary choices can improve patients' outcomes—and lives.

BY STEVEN G. PRATT, MD, STUART RICHER, OD, PhD, DENNIS RUSKIN, OD, AND KERRY GELB, OD

Most people would agree that nutrition is a cornerstone of good health. The right vitamins, minerals and nutrients help to safeguard our vision and senses for a lifetime and aid in peak brain function. In particular, 'superfood' components mitigate many of the changes that occur in our bodies over time. These are rich in antioxidants and anti-inflammatories, the vitamins and minerals that keep our hearts and lungs healthy into our senior years, protect our vision and keep our minds sharp. Not only can the right nutritional choices optimize patients' eye health and vision over the lifecycle, they also help to keep free-radical damage and disease at bay.

Research continues to validate why good nutrition should be an integral part of eye care. This article delves into the relationship between what we eat and how we see.

SUPERFOOD DEFENSE AGAINST DEGENERATIVE & OXIDATIVE PROCESSES

It's important for patients to load up on superfood nutrients to help preserve their eyesight into their senior years. To qualify as a superfood, it has to be readily available, with a significant number of scientific publications verifying the power of the food (specifically, its nutrients) to prevent disease and promote wellness and longevity. Here are some top performers to include in the diet:

Pomegranate juice can stimulate vasodilation, which increases blood flow. One manifestation of age-related macular degeneration (AMD) is reduced blood flow to the eye. Cellular metabolism depends on adequate oxygen and nutrients as well as proper elimination of waste products. Improving blood flow to an organ system helps it stay in good health. Pomegranates are also phytochemical heavyweights; these fruits have two to three times the antioxidant power of green tea or red wine and also possess potent anti-inflammatory chemicals.[1]

Walnuts have a high concentration of omega-3 fats. The fluid and flexible characteristics of omega-3 fats maximize cells' abilities to absorb their nutrients and eliminate wastes. In addition, the alpha-lipoic acid (ALA) and other polyphenols in walnuts act as antioxidants to block adverse cellular signals from free-radical exposure that can increase inflammation. Walnuts may even help prevent AMD progression. A study in *Archives of Ophthalmology* found that individuals who ate more than one serving of nuts a week decreased their risk of AMD progression by more than 50%.[2]

A 10-point Plan to Prevent AMD

1. Avoid smoking, weight gain, high glycemic index foods, high fructose corn syrup, soda and sweetened drinks, artificial sweeteners, dairy, grain-fed meat and trans fats.
2. Eat foods with omega-3s and/or take supplements.
3. Embrace an anti-inflammatory or paleo diet.
4. Eat foods that contain lutein and zeaxanthin.
5. Drink 1.5 liters of water a day with green tea and lemon.
6. Include spices such as cinnamon, rosemary, oregano, garlic powder, Himalayan salt, turmeric (contains curcumin), ginger and paprika.
7. Maintain optimal vitamin D3 blood levels.
8. Get regular exercise and use stress reduction strategies.
9. Take supplements for ocular nutrition.
10. Undergo a regular retinal and macular pigment density exam.

Spinach is dense with carotenoids such as lutein and zeaxanthin that act as powerful antioxidants to fight free radicals, as well as anti-inflammatories that can help reduce the risk of age-related eye disorders. The Nurses' Health Study showed that participants who consumed raw or cooked spinach at least twice a week lowered their cataract risk by up to 38% compared with those who consumed spinach less than once a month.[3]

Kiwis are an excellent non-leafy source of lutein and zeaxanthin. Their high vitamin C content also acts as a water-soluble antioxidant to help neutralize free radicals that damage cells and lead to inflammation.

Oranges are naturally rich in folate, a B vitamin. Folate facilitates processing of the amino acid homocysteine, which, when elevated, promotes atherosclerosis and inflammation. High homocysteine levels have been linked to increased risk of AMD and cardiovascular disease, and potentially Alzheimer's disease.[4-7] Food folate along with vitamins B6 and B12 work together to lower homocysteine levels and oxidative stress. Folic acid is the synthetic form of food folate, which in high doses may be problematic for genetic 'under-methylators' in the population.[8]

Choline and betaine prevent the buildup of homocysteine, promote proper cell membrane function and assist in nerve-muscle communication. Good sources of choline include eggs, cod, shrimp, navy beans, salmon, Brussels sprouts, broccoli and kidney beans. Good sources of betaine include wheat bran, quinoa, beets and spinach.

Anti-inflammatory foods are important to maintaining vision health, since research reveals that ocular surface inflammation can contribute to the destabilization of the tear film. We now know that ocular surface disease and dry eye amplify hyperosmolarity either directly or by inducing a cascade of inflammatory events.[9] Standout anti-inflammatory foods include wild salmon and Alaskan/northern halibut, canned chunk light or albacore tuna, mackerel, sardines, farmed trout, herring, oysters and clams.

Since antioxidants also tamp down inflammation, it's important to include free radical-fighting foods such as blueberries and their "sidekicks" purple grapes, cranberries, boysenberries, raspberries, strawberries, pomegranates, plums, extra virgin olive oil and nearly every spice.

Antioxidant-packed foods are essential to maintaining good eye health and vision for a lifetime. The health of the macula is enhanced as a result of the antioxidant and anti-inflammatory properties of the macular pigment—a collection of three dietary carotenoids found in equal concentrations in the macula: lutein, zeaxanthin and mesozeaxanthin.

10 Foods that Fight AMD

1. Pastured eggs
2. Leafy green vegetables (e.g., spinach, kale, collard greens)
3. Garlic
4. Green vegetables (e.g., broccoli, bell pepper, Brussels sprouts)
5. Wild-caught fish (salmon, sardines, anchovies and mackerel)
6. Oranges
7. Goji berries
8. Orange peppers
9. Mediterranean diet
10. Sweet potatoes

Sources of lutein include green leafy vegetables such as spinach, kale, collard greens, Swiss chard, arugula, mustard and turnip greens, bok choy, romaine lettuce, seaweed and purslane.

Sources of zeaxanthin include orange bell peppers, goji berries, yellow corn and cornmeal.

Sources of mesozeaxanthin include salmon skin, sardine skin, trout skin and trout flesh, albeit in minute quantities.

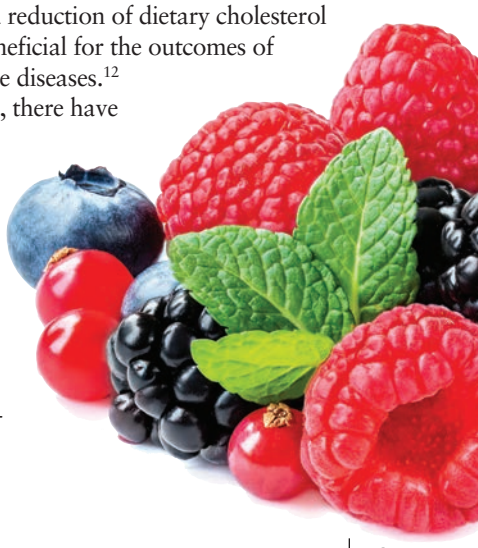
The guidelines provided here merely scratch the surface of proper nutrition habits. These concepts are developed extensively in the five books Dr. Pratt has written on the topic of superfoods.

USING WELLNESS TO IMPROVE GLAUCOMA MANAGEMENT

The pathophysiology of glaucoma offers a number of opportunities to intervene through a wellness paradigm. This may include combining traditional pharmaceutical strategies and drainage devices designed to lower intraocular pressure with walking and exercise, as well as approaches to maintain higher optic nerve perfusion pressure, reduce oxidative stress on the trabecular meshwork and optic nerve, and provide neuroprotection to retinal ganglion cells and associated optic nerve head tissues.[10,11]

Research shows that antioxidants play a role in mitigating the myriad processes leading to the development of many diseases.[12] In one study, diets rich in fruits and vegetables appeared to be protective against glaucoma, cataracts and AMD, while diets higher in meat and nuts possibly increased the risk of oxidative stress-related eye diseases.[12] In the same study, higher intake of vitamin C and β-carotene from food and reduction of dietary cholesterol intake were seen to be beneficial for the outcomes of oxidative stress-related eye diseases.[12]

In the last several years, there have been limited therapeutic options beyond IOP reduction. Researchers and clinicians have shown a renewed interest in applying the principles of preventative ocular wellness to counteract glaucoma, including timing of hypertensive medications and



addressing sleep apnea and excessive sleeping. This holistic approach to disease, along with DNA genetic markers and personalized epigenetic medicine, should play a much greater role in fighting the disease in the future.[13]

VITAMIN C'S IMPACT ON IOP

A seminal 2019 study combined metabolomic and genetic data to identify metabolic processes that modulate IOP in healthy populations.[14] It found that O-methylascorbate, a circulating vitamin C metabolite, had a significant IOP-lowering effect, consistent with existing knowledge of the antihypertensive and antioxidative role of ascorbate compounds.[14] The naturally occurring metabolite is minimally cytotoxic and has a strong reductive capacity against photo-oxidative stress, which might play a role in trabecular meshwork degradation due to aging.

Bioflavonoids—highly hydroxylated polyphenols—extend the half-life of ascorbic acid and appear to play a role in lowering IOP. One commercial product, Mirtogenol, contains two of these substances (80mg bilberry/Vaccinium myrtillus L and 40mg pycnogenol or French maritime bark extract/Pinus pinaster). Mirtogenol was found to lower IOP on its own and in combination with traditional glaucoma drops, in two small studies.[15,16] A second product, Formula 216, is a form of vitamin C that can be taken once per day yet doubles the serum molar concentration of vitamin C.

NUTRIENTS AIDING OPTIC NERVE PERFUSION

In the Maracaibo Aging Study, extreme reductions in nocturnal systolic and diastolic blood pressure (>20% compared with daytime blood pressure) in a Hispanic population were significant risk factors for glaucomatous damage, with dramatic odds ratios of 19.78 and 5.55, respectively.[17]

Virtually all of the B vitamins align with the goal of physiologically enhancing optic nerve perfusion and mitochondrial-targeted ophthalmic nutrients. Vitamin B1 (thiamin) is necessary for glucose metabolism; it plays a key

Addressing the Growth of AMD with Nutrition

AMD is the leading cause of irreversible vision loss in developed nations and is anticipated to affect 196 million people worldwide by 2020, yet the etiology of this disease remains unknown.[1] We believe nutrition plays a pivotal role in helping patients find new ways to treat this disease.

AMD & Nutrition

In 2017, a transformative paper was published on the origin of AMD and its ties to nutrition and wellness.[1] The authors, who had sought to estimate AMD prevalence, noted that between the years 1851 and 1930, AMD was a medical rarity worldwide.[1] Its prevalence rose modestly in the 1930s in the US and UK and reached epidemic proportions in the US by 1975.[1] Simultaneously, between 1880 and 2009, processed, nutrient-deficient foods gradually supplanted and displaced whole, unprocessed, nutrient-dense foods in developed nations.[1] By 2009, 63% of the American diet was made up of nutrient-deficient foods in the form of refined white flour, added sugars, vegetable oils and artificially created trans-fats.[1]

Correlative data in 25 nations showed that increasing sugar and polyunsaturated oil consumption was associated with new onset or rising prevalence of AMD, generally within 30 to 40 years of the start of greater processed food consumption.[1] The study supported its hypothesis that processed, nutrient-deficient foods were the primary and proximate cause of AMD.[1] The authors added that the study also indicated macular degeneration was entirely preventable through dietary strategies and avoidance of processed foods, and the research had implications for patients with early and intermediate AMD.[1]

AMD Diagnosis

With this in mind, we believe that AMD technology for early detection should include dark adaptation, macular pigment optical density, ForeseeHome's Preferential Hyperacuity Perimetry technology, SD-OCT and genetic testing. Once a patient is determined to be at risk, prevention strategies are essential to decrease the disease burden. It's important to note that AMD is not only an ocular disease, but also a systemic vascular disease and can be associated with cardiovascular disease.[2] SD-OCT angiography can provide valuable information concerning the state of the choriocapillaris.

AMD Prevention

Our goal should be to prevent AMD from developing in the first place. Omega-3 fatty acids, according to many studies, can decrease the risk of macular degeneration. A meta-analysis study from *Archives of Ophthalmology* showed that a high dietary intake of omega-3 fatty acids was associated with a 38% reduction in the risk of late macular degeneration.[3] Many reputable companies provide high-quality omega-3 supplements, and a quick and inexpensive red blood cell omega-3 index test can indicate whether or not a patient is replete.

Many quality ocular supplements also are now available to decrease AMD risk. It's important to use supplements that are well researched. Selling supplements in the office is an ideal way to ensure that patients are getting a high-quality product with evidence-based medicine behind it.

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10 Foods to Help Prevent Diabetes

1. Raw nuts and seeds (e.g., walnuts)
2. Organic vegetables (e.g., broccoli)
3. Organic spices (e.g., turmeric [contains curcumin], ginger, rosemary, oregano, paprika)
4. Raw cacao
5. Wild-caught fish (e.g., sardines, anchovies, herring, mackerel, fish roe)
6. Avocado and healthy fats
7. Organic berries
8. Flaxseeds and chia seeds
9. Organic chicken and turkey
10. Fermented vegetables (e.g., sauerkraut, kimchi)

role in nerve, muscle and heart function and helps offset the excess sugar, caffeine and alcohol in the US diet. Vitamin B2 (riboflavin) is involved with glutathione (GSH) intracellular redox state maintenance. Vitamin B3 (NAD from niacinamide or nicotinamide riboside) plays a part in the viability of mitochondria.[18,19] Vitamin B5 (pantothenic acid) modulates adrenal health and potential ascorbate depletion. Vitamin B6 and methyl-folate (from natural food folate) and vitamin B12 help lower the vascular oxidant homocysteine. Biotin is involved in fatty acid metabolism. (All these nutrients are reduced in patients taking OTC or prescribed proton pump inhibitors for acid indigestion and GERD.)

Magnesium, which can be a factor in compromised vascular health, has been shown to improve blood flow by modifying endothelial function and endothelial nitric oxide pathways.[20] Magnesium exhibits a neuroprotective role by blocking N-methyl-D-aspartate receptor-related calcium influx and inhibiting the release of glutamate, yielding a cell-protective role against oxidative stress and apoptosis.[20]

BOOSTING MITOCHONDRIAL FUNCTION

One new approach to glaucoma management aligns with the idea that bioenergetic dysfunction lies at the nexus of genetic and environmental causes of diseases.[21,22] In this model, mitochondrial health and modulation form the underpinnings of good health. This regulation reaches far beyond energy production and includes oxidant and antioxidant redox balance, signal transduction via reactive oxygen species, calcium homeostasis, cell death (apoptosis) and the epigenomic regulation of genes.

Some optometrists may be aware that Leber's hereditary optic atrophy, retinitis pigmentosa and chronic progressive external ophthalmoplegia are all caused by direct damage to mitochondrial function, induced by defective genes.[23] Studies also show that, as mitochondrial energy dwindles with age, organ-specific damage can occur with varying phenotypic expression, dependent upon the supply of oxygen and the health of mitochondria.[24,25]

One approach to age- and pharmaceutical-associated (e.g., beta-blockers, statins) loss of mitochondrial function is to supply nutrients associated with energy production. These include N-acetyl cysteine, acetyl-L-carnitine, alpha lipoic acid, ubiquinone and pyrroloquinoline quinone. Magnesium, niacin (as niacinamide) and myriad bioflavonoids found in bilberries, pycnogenol, red wine (resveratrol), grape seeds, black currant fruit, quercetin (found in red onions, apples and wine), gingko biloba leaf and saffron bulbs may all be helpful.

From our perspective, proactively addressing and managing glaucoma will require more attention to the nuances of blood pressure and ocular nerve head perfusion. Proper sleep, exercise, stress reduction and preserving key energy pathways in the body are also essential to promoting peak ocular health when it comes to managing a disease such as glaucoma.

TAKING AIM AT AMD

AMD continues to be the leading cause of irreversible blindness in adults older than 50 in North America.[26] Many of the genetic and environmental risk factors such as high sugar intake, low vitamin D status, high red meat heme consumption (iron), high homocysteine, excessive calcium supplementation and copper plumbing are all potentially associated with AMD as well as with other complex degenerative diseases of advanced age, such as cardiovascular disease and Alzheimer's disease.[27] Neovascular AMD (nvAMD)—an advanced form of macular degeneration—creates an enormous societal burden and negatively affects patient quality of life.

As well as the physical toll of AMD for the patient, the disease's complex management requires a substantial time investment by physicians, staff, patients and caregivers.[28] Furthermore, the expensive nature of anti-VEGF drugs may be financially unsustainable over time.[29] And the drugs' tendency to increase IOP is another incentive to seek out alternatives.[30]

As disease preventionists, optometrists strive to prevent or delay AMD from progressing to nvAMD. Modern

technology enables the detection of early AMD progression so referrals can be made when necessary. However, this is only half of the management story; the other half is having a discussion with high-risk patients about a nutrition and lifestyle plan that is customized to their personalized health care needs. Minimizing the progression of nvAMD begins with the knowledge that prevention always trumps tertiary care; anti-VEGF treatment should be a patients' last line of defense, not their first.

A New Model of Practice

As our health care model continues to evolve, optometric and medical practices of the future may look very different. The following is a snapshot of the OD and MD practices of three OWNS board members from the East Coast, Midwest and West Coast:

• ***Kerry Gelb, OD, LensCrafters, Woodbridge, NJ.*** During conversations with patients about their conditions, I give patients an option: "Would you like me to teach you how to treat the root cause, or just treat your symptoms?" The response is usually for me to help treat the root cause, with ensuing comments such as, "Why hasn't my primary doctor spoken to me about this subject?" It's important to first explain to patients that nutrition and lifestyle medicine are adjuncts of traditional symptoms-based treatments. Patients must also understand that early diagnosis usually translates into better eventual outcomes and can reduce the need for expensive and chronic medication use.

I have created comprehensive nutrition plans for patients with AMD, diabetes and DED. And I advise other optometrists interested in adding a functional medicine component to their practices to create similar plans for common ocular conditions associated with nutrition and lifestyle medicine. Eye care professionals should also reach out to doctors in other specialties who practice preventive functional medicine as a way to build the practice and obtain referrals. In fact, I receive most of my referrals from like-minded MDs.

• ***Steven G. Pratt, MD, La Jolla Laser Vision, La Jolla, Calif.*** My surgical practice is an extension of my personal experiences with macular degeneration and subsequent nutrition and wellness practices, outlined in my trademarked SuperFoodsRx products. I and my practice colleagues promote natural and active outdoor living. And my website, www.superhealthyliving.com, provides patients with access to free pamphlets and handouts to learn about natural ways to help prevent macular degeneration and migraine headaches, manage dry eye and heal wounds. The site also offers tips about supplements and has a section for pet health, and individuals can purchase my books, such as the latest, *SuperFoodsRx for Pregnancy: The Right Choices for a Healthy, Smart, Super Baby*.

• ***Stuart Richer, OD, PhD, Captain James A. Lovell Federal Health Care Facility, North Chicago.*** I work on behalf of veterans and active duty US Navy military personnel at one of the largest US federal health care centers in the country. In the office, I rely on props (e.g., cans of spinach, sardines, low-salt V8, plastic berries) and single-page educational handouts to directly educate patients. During weekly lectures and department-wide email blasts, I encourage other staff members, residents and optometry and medical students to practice preventive ocular medicine.

PATHOGENESIS OF nvAMD

Our understanding of the pathogenesis of AMD has evolved over the last 18 years since the publishing of the Age-Related Eye Disease Study (AREDS 1).[31] From a historical perspective, the earliest reference to nvAMD is from Junius and Kuhnt, who first described hemorrhagic macular lesions in 1926.[32] This disease observation was later termed senile disciform macular degeneration. Initially, no treatment was available for the disease, as photodynamic therapy using verteporfin and other anti-VEGF therapy had not been developed yet.

In the early 1990s, the AREDS 1 randomized clinical study was designed to determine AMD progression rates after participants were assigned to take an antioxidant formulation of vitamins or placebo.[31] Patients who progressed to advanced AMD were considered to be at the end stage of AMD. Advanced AMD indicates progression to two distinct clinical end-points—nvAMD or geographic atrophy (GA). For convenience, and because both diseases were untreatable at the time of the study's start, the conditions were lumped together as a common endpoint.

AREDS was formulated specifically for nvAMD and is not effective in a setting of GA. The conclusion that Johanna Seddon reached in a 2016 paper—that the effectiveness of antioxidant and zinc supplementation appeared to differ by genotype—was a cautionary note to the scientific community that AREDS analysis should not include GA, as it will dilute and obscure meaningful relationships related to nvAMD progression rates.[33]

Age-related changes that predispose individuals to AMD occur in the posterior segment that includes the photoreceptors, retinal pigment epithelium (RPE), Bruch's membrane and choriocapillaris; these alterations potentially cause a lack of homeostasis and dysregulation of the "complement" system, although specific mechanisms have yet to be determined.[34] Researchers at the Wilmer Eye Institute found that a combination of impaired complement regulators can result in inadequately controlled complement by the RPE in AMD, which induces RPE damage; drusen are a by-product of complement-mediated inflammatory processes.[34] As such, patients who have unregulated complement activation can be at risk for producing angiogenic growth factors leading to nvAMD.

Lifestyle triggers that change the rate of progression to nvAMD include nutritional and epigenetic factors (see, "A 10-point Plan to Prevent AMD"). Dr Richer has also published several peer-reviewed papers concerning the

science of epigenetics and the prescription of Longevinex to improve visual function (including dark adaptation) and retinal structure (including stem cell regeneration) in patients into their 90s.[27]

NUTRIENTS, GENETICS AND PROGRESSION

Various studies demonstrate a link between diet and progression to AMD. The Eye Risk Consortium study revealed that adherence to the Mediterranean diet was associated with a 41% reduced risk in nvAMD.[35] The findings supported the role of a diet laden with nutrient-rich foods such as fruits, vegetables, legumes and fish in the prevention of AMD. In June 2018, Chapman et al. performed a systematic review of significant long-term studies intended to evaluate the role of diet and food intake in AMD.[36] Negative drivers contributing to an increase in progression risk to nvAMD of between 56% and 270% included choosing a high dietary glycemic index diet, eating processed meat and consuming a typical Western diet.[36] High consumption of vegetables rich in carotenoids and fish containing omega-3 fatty acids was beneficial for those at risk of AMD.[36]

Though genetics play a role in eye and overall health, wellness or disease is greatly dependent upon desirable or undesirable biological activities interacting with those genetics. The CFH gene provides instructions for making protein complement factor H, used to help regulate the body's immune response. Lechanteur et al. showed that patients who had high-risk CFH risk alleles had a reduced timeline for pathogenesis to nvAMD by 12.2 years.[37] Millen et al. reported that blood levels pointing to vitamin D deficiency were associated with a 1.8-fold increase in the odds of having AMD among women with low-risk CFH, and rose to a seven-fold increase in women with high-risk CFH, suggesting a synergistic effect between vitamin D status and complement cascade protein function.[38]

Another study, CAREDS, reported that diets rich in lutein plus zeaxanthin might protect against intermediate AMD in healthy women younger than 75 years.[39]

The power of good nutrition is a top priority in reducing the progression to nvAMD. Supplements should be considered as a backup to core nutritional practices to prevent or reduce nvAMD (see, "10 Foods that Fight AMD").

THE PUBLIC HEALTH CHALLENGE

Nutrition and lifestyle medicine are not new concepts to those of us at the OWNS. Yet, it still surprises us how unfamiliar these ideas are for many of our patients and new graduates and how much interest they express in learning more. A growing body of research is revealing the importance of such a strategy.

A 2019 study in *The Lancet* showed that, globally, one-fifth of all deaths were associated with poor diets.[40] In addition, more than 90% of Americans are deficient in at least one nutrient, based on our estimates from USDA survey findings and CDC Nutrition Report data. A staggering 63% of food consumed in the US is processed, with only 12% of food coming from plant sources; the remaining 25% comes from animal sources.[41] We at the OWNS believe that minimizing processed, manufactured food and exchanging it with whole, organic food is the single most important factor in improving ocular and overall health through reducing inflammation—the core component of chronic disease.

A 2016 report and review of 12 major epidemiological studies as well as the 2010 United States Census population estimated that more than half of the US population over age 40—about 90 million of 142 million adults—experienced vision problems due to eye diseases such as AMD, cataracts, diabetic retinopathy and glaucoma, in addition to vision impairment, blindness and refractive error.[42]

Foods to Help Prevent Dry Eye Disease

1. Raw nuts and seeds (e.g., walnuts, pine nuts, macadamia nuts, flaxseed, chia seeds, pumpkin seeds)
2. Organic fruits/vegetables (e.g., kale, spinach, Swiss chard, strawberries, goji berries, acerola cherries, blueberries)
3. Organic spices (e.g., turmeric [contains curcumin], ginger, paprika, rosemary, oregano, pumpkin spice, clove)
4. Gamma-linolenic acid foods (e.g., black currant seed oil, blue-green algae [e.g., spirulina], borage oil, hemp seeds)
5. Omega-3 fatty acids (e.g., wild salmon, anchovies, mackerel, sardines)
6. Avocado
7. Organic green tea
8. Pastured eggs
9. Organic chicken and turkey
10. Broccoli and antioxidant-rich cruciferous vegetables (e.g., cauliflower, Brussels sprouts, red cabbage, kale, collards, watercress, mustard greens)

PUT WELLNESS ON THE MENU

We at the OWNS strongly believe that AMD and diabetic macular edema (DME) are heavily associated with poor nutrition and lifestyle choices. And yet, at the same time, traditional medical procedures continue to skyrocket. For example, the number of intravitreal injections (IVIs) for conditions such as AMD and DME are seeing an exponential rise.[43] A total of 5.9 million IVIs were performed in the US in 2016.[44] This is up dramatically from less than 5,000 IVIs between 1997 and 2001.[45]

Unfortunately, medical and optometry schools are not evolving to reflect a changing wellness landscape. Their philosophies and curricula continue to center upon symptoms-based medicine rather than addressing root causes. Optometrists are provided with little to no training in nutrition and lifestyle medicine. Fortunately, the OWNS is cataloging years of research and lectures on ocular nutrition and wellness. And various doctors around the country have played a role in creating valuable ocular nutrition content online for patients. ❍

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Two Big Controversies in Ocular Nutrition

AMD supplements and omega-3s are both still in the hot seat.

BY STUART RICHER, OD, PHD, AND DENNIS RUSKIN, OD

The idea that proper diet and vitamin supplementation can improve ocular health is a given these days, as research showcases the positive effects certain nutrients can have on conditions such as age-related macular degeneration (AMD) and cataracts. Despite the progress made by a greater understanding of nutrition and the eye, some fierce debates continue to rage on in the optometric community.

Here's a look at two red-hot topics in ocular nutrition.

ROUND 1: IS RESPONSE TO AREDS AFFECTED BY GENETICS?

When the Age-related Eye Disease Study (AREDS) first published nearly two decades ago, the promise that an oral supplement could reduce the risk of AMD progression was big news.[1] The formulation was patented and PreserVision was born. The formulation was shown to reduce the risk of progression by some 25% and it became the standard of care for moderate AMD.

As the genes associated with AMD were discovered over the following decade, researchers asked the question, "Do all patients responded similarly?" This led to eight subsequent publications.[2-9]

Four of the publications measured AMD progression to either geographic atrophy (GA) or to choroidal neovascularization (CNV).[2-5] However, a 2016 study reminded everyone that the AREDS formulation was only shown to be effective against progression to CNV and not against GA.[6] The study demonstrated a statistically significant interaction between genetics and the AREDS formulation against progression to CNV.[6] Thus, the four publications incorrectly measured progression to GA.[2-5] This might be analogous to studying Lucentis (ranibizumab, Genentech) against GA and CNV when we know that it is only effective against CNV. This mistake clouded the truth and created intense confusion among practitioners.

The last four research studies all focused on progression to CNV, and all four noted a statistically significant gene

Riddle of the Zincs

Zinc, a necessary but otherwise unassuming mineral, was thrust center-stage in the controversy over the AREDS data. Currently, no reliable evidence exists to confirm that 25mg of zinc oxide is safer than 80mg in an AREDS formula. Ananda S. Prasad, MD, the reigning authority on zinc therapeutics and supplementation, advises that 45mg of oral zinc can be consumed without creating a zinc/copper imbalance.[1] Zinc deficiency is a real concern, with 29% of the US population experiencing inadequate intake (91 million out of a population of 314 million).

However, there is more to this zinc story. Zinc is poorly absorbed, especially the AREDS zinc oxide form, which is insoluble in water. This is often due to a lack of stomach acid. Co-administration of zinc with vitamin B6 increases absorption substantially. Once absorbed, zinc is bound to metallothionein to make sure it doesn't get out of control, being a metallic mineral. Co-consumption of zinc with selenium releases zinc from metallothionein, its binding protein. These nutrient dynamics all influence whether therapy is harmful, has a null effect or is beneficial. Clearly, more research is needed to examine these relationships.

A host of clinical factors that complicate the zinc debate such as age-related hypochlorhydria, concurrent chronic use of over-the-counter and pharmacologic acid blockers, competing iron and copper intake as well as *H. Pylori* infection will all effect zinc bioavailability in your patient.

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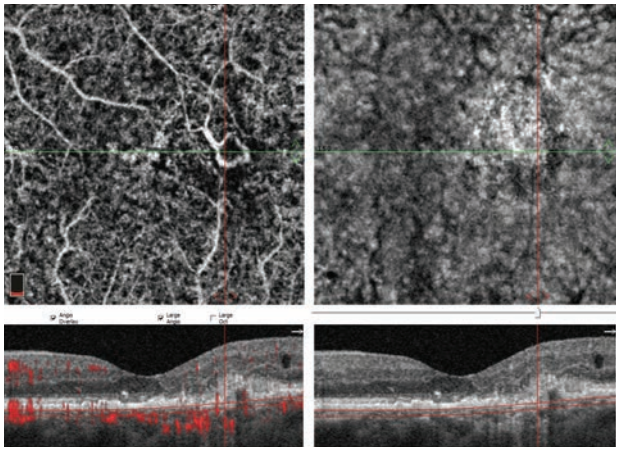
Photo: Steven Ferrucci, OD



Many moderate AMD patients who take the AREDS or AREDS2 formulation can sigificantly reduce their risk of progression, though a specific genotype increases risk of CNV development in 15% of cases.

interaction.[6-9] In the most recent analysis, the independent authors studied 266 patients and found that patients were four times more likely to have progressed to CNV if they had a specific genotype and took the AREDS/AREDS2 formulation.[9]

The data now seems clear. The AREDS/AREDS2 formulation is a valuable product for most people with moderate AMD. Many patients with certain genotypes can experience a greater than 50% reduction in their risk for progression to CNV. No other formulation has been shown to do that. However, approximately 15% of patients with a specific genotype experience a three- to four-fold increased progression to CNV. Thus begins the era of personalized medicine in AMD for those of us who manage these patients. As practitioners we are now armed with the knowledge necessary to improve patient outcomes, perhaps through improved compliance for those who benefit from the formulation and to limit AREDS/AREDS2 use in those who will not benefit.

ROUND 2: THE DREAM STUDY VS. FISH OIL

For more than a decade, many eye care practitioners have enthusiastically recommended omega-3 fatty acid supplements to their dry eye patients to alleviate symptoms without the double-edged sword of adverse side effects.

But in May 2018, the Dry Eye Assessment and Management (DREAM) study seemed to take the wind out of the sails of fish oil's effectiveness, since the investigation reported omega-3s offered no benefit over the olive oil placebo.[10]

This rocked some corners of the profession, especially for those who touted the well-established treatment. While some backed away from omega 3s after these results, experts cautioned to take a closer look at the study instead of just skimming the headlines.

Fish oil as a treatment for dry eye first came about in a 2005 study.[11] It showed women who ate regular amounts of tuna in their diets had lower rates of dry eye symptoms.[11]

Further proof came along in 2011 in the form of a pilot study that concluded dietary supplementation with omega-3 fatty acids in dry eye showed no significant effect in meibum lipid composition or aqueous tear evaporation rate.[12] Yet it also reported the average tear production and tear volume were increased in the omega-3 group.[12]

The DREAM study was a one-year, double-masked, randomized, multicenter study by the National Eye Institute that looked at the benefits of omega-3 supplements in dry eye patients.[10] Patients were allowed to continue their current treatments, which is not the case in most industry-sponsored trials of dry eye treatments.

Eligible participants included those who had signs and symptoms of moderate-to-severe dry eye on two consecutive exams performed two weeks apart, dry eye symptoms for at least six months, an Ocular Surface Disease Index (OSDI) score ranging from 25 to 80 at a screening visit and an OSDI score ranging from 21 to 80 at the baseline eligibility visit.[10] Patients also had to be willing to continue their current dry eye treatment regimens, be using or want to use artificial tears at least twice daily in the previous two weeks and had other dry eye symptoms.

Basically, the "real world" clinical trial included patients with typical dry eye disease who continued to seek relief of symptoms despite the use of other interventions.

Additionally, patients with a history of thyroid disease, Sjögren's syndrome, rheumatoid arthritis or inflammatory diseases could be included in the trial if they were otherwise eligible.

The 3,000mg daily dosage of omega-3 fatty acids was the highest dose used to date in clinical trials of fish-derived omega-3 fatty acids.[10] The daily placebo was approximately one tablespoon of olive oil, which primarily delivered n-9 oleic acid, a substance usually considered neutral with respect to changes in signs and symptoms of dry eye.[10]

After 12 months, the study authors did not find significant differences in mean OSDI or conjunctival staining, corneal staining, tear break-up time and Schirmer's test between groups.[10]

Since the DREAM study's release, some have cried foul over certain aspects of the investigation's methodology, especially the olive oil placebo, citing its potential therapeutic effects. Still others took issue with the study's "real world" approach and the fact patients were allowed to continue taking their medications.

The DREAM investigators vigorously defended their choice of the olive oil placebo. They cited the Mediterranean diet, which includes an average of 60g of olive oil, and compared it with their olive oil placebo dose (5g, the equivalent of one tablespoon teaspoon) which they countered was too low to have a therapeutic effect.[13,14]

The researchers continued on the defense by arguing defensively that the anti-inflammatory effects associated with olive oil are attributed mainly to polyphenols not found in the refined olive oil used in the study.[15] However, research does show that oleic acid can alter the microbiome and reduce dysbiosis, conferring anti-inflammatory effects elsewhere in the body.[15] Oleic acid can also counter the negative impact of saturated fat on the microbiome.[16]

Others in the profession called out the study's loose inclusion and exclusion criteria. The fact that the study allowed moderate-to-severe dye eye patients of different demographics and health profiles made it increasingly difficult to come to a definitive conclusion that all oral omegas were ineffective, the opposition argued.

Despite the criticism, the DREAM research team has doubled-down. During a presentation at ARVO's 2019 meeting, the study's researchers presented a follow-up investigation that found no significant differences in outcomes between patients who stopped taking the fish oil supplements and those who continued taking them over an additional 12-month period.[17] The DREAM investigators said this reaffirmed their original study results of no demonstrable benefit from omega-3 supplements.[17]

While the research battle rages on, practicing clinicians who have found success with omega-3s will likely take the DREAM study with a grain of salt, and others will believe the study reinforced recommending a gamma linolenic acid along with fish oil. ❍

Eights Threats to Counter

Here are major disruptors of modern health that challenge our well-being and drain our vitality if we are sensitive (i.e., immune intolerant) or exposed chronically without offsetting or balancing wellness strategies. However, opinions differ among experts on a number of these, and it can be difficult to effect change in mindset and behavior among some doctors, let alone patients.

- Lectins
- Soy products
- Broad-spectrum antibiotics
- NSAIDs
- Gastrointestinal acid blockers
- Artificial sweeteners
- Hormone disruptors
- Herbicides

Two of these deserve extra attention:

Lectins: Steven Gundry's *The Plant Paradox* reveals a danger in the American diet: a toxic protein in plants called lectins.[1] These proteins are found in hundreds of common foods, including 'nightshade' vegetables belonging to the 2,000+ species Solanaceae family which includes common vegetables (e.g., eggplant, tomatoes, peppers, potatoes). This is why it is important to focus on building one's immune tolerance.

Soy Products: This nutrient can be problematic in two ways. First, soy contains phytoestrogens that mimic estrogen, prompting the body (both female and male) to store fat by leading to disruption of the adrenal and thyroid glands. Thus this 'toxic superfood' can increase our body weight, change our body shape and impact our fertility. Second, soy contains goitrogens—substances that depress our thyroid gland function, making us sluggish, decreasing our concentration and sex drive.

Taken together, 21st century challenges such as lectin and soy sensitivity affect our digestion, immune competence, cognitive status, reproductive potential and even increase our susceptibility to cancer, cardiovascular and oculovascular diseases.

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