A Supplement to REVIEW OF OPTOMETRY

WELLNESS ESSENTIALS
FOR CLINICAL PRACTICE

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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OWNS

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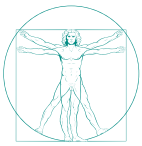


Reach for Health, Not Disease

Too often, doctors approach 21st century challenges with 19th century thinking.

FROM THE BOARD OF THE OCULAR WELLNESS & NUTRITION SOCIETY

Modern humans are facing an array of vulnerabilities and disruptors. Yet there is a bias in allopathic medicine to pathologize and medicalize healthcare. This mindset arises from a view that our genetics dooms us to a life beset by disease, with the appropriate response being 'crisis' medical intervention.

In addition to burdening society with an enormous healthcare infrastructure, this orientation runs counter to the new science of epigenetics. We now know, for instance, that we exist in a symbiotic relationship with gastrointestinal microbes. There are an immense number of deadly microbiome disruptors, including broad-spectrum antibiotics, some genetically modified foods, chronic stomach acid blockade, natural and artificially sweeteners, hormone disruptors and blue light. Modern environments further weaken our immune system by bombarding us with disease-causing toxins and pollutants.

If your patient is juggling multiple diseases and doctor appointments or taking more than nine medications (i.e., polypharmacy), their doctors are likely 'dropping the ball.' Americans are now dying from this dysfunctional disease-centered care system.

As optometrists, we examine 120 million patients per year, and it is the strength of our knowledge of biology that will reverse these trends.

Modern medicine has awoken to the power of nutrition in modulating cardiovascular health outcomes, as reflected in recent statements from the *Journal of the American Medical Association*: "Recommended dietary patterns now focus on meals high in vegetables, fruit, whole grains, seafood, legumes and nuts that are moderate in low-fat and non-fat dairy products, that are lower in red and processed meat, and foods and beverages containing added sugar, and refined grains."[1]

However, despite having more doctors, hospitals and gyms than any other country, Americans are obese, life expectancy has begun declining year over year and hard-fought gains in life expectancy have now begun to be lost.

CHANGING MINDS AND METHODS

As a board, the Ocular Health and Wellness Society (OWNS) believes the body can heal and recover, and become stronger than before, if provided with the panoply of raw materials all mammalians require to thrive. Avoidance of disease through prudent lifestyle modifications is far better for the individual and society. As doctors, we can often spare patients the misery and fear that accompany medical intervention, but doing so takes a commitment to address healthful living with all patients, even the healthiest ones.

"You know what's the biggest, 'Oh, wow!' about getting your eyes examined?" asks Kerry Gelb, OD (above left), in a trailer for his documentary *Open Your Eyes*. "People just don't realize that the eye is a biomarker for many diseases—there's over 170 systemic diseases that can manifest in the eye." The documentary is available at openyoureyes2020.com.

REACH FOR HEALTH, NOT DISEASE

Optometrists aren't accustomed to this, nor are we typically trained in health and wellness during our professional education. Like so many health care providers, we are the product of the disease-focused culture of medical practice.

This disconnect between patient need and professional preparation was the impetus for founding president Dr. Jeffrey Anshel to create OWNS. As a nine-year-old subspecialty society, it encompasses just 1% of the optometric profession, along with several ophthalmologists and PhDs. Our mission: to provide leadership, education, advice and guidance to eye care professionals and consumers regarding wellness, eye health and vision. OWNS supports evidence-based analysis on the entire wellness spectrum, including nutrition. We endorse no specific products.

OWNS sponsors two national symposia each year, generates print and online materials and promotes the inclusion of nutrition education/preventive ocular health care in the curricula of optometry institutions. We are grateful to progressive Emeritus Professor Gerald A. Franzel and Dean Larry Davis at the University of Missouri, St. Louis College of Optometry for hosting our 12-hour CE Ocular Nutrition Weekend, now in its 12th year.

And one exciting addition to the society's toolbox is this new supplement, produced in conjunction with *Review of Optometry* and made possible by an unrestricted educational grant from Bausch + Lomb.

In this guide, we show what OWNS has learned about restoring health rather than fighting disease. We want you to put treatment of eye disease away for a brief moment and rediscover the 'language of health.' This requires a shift in thinking from descriptive pathology and symptomatology to focusing on well-functioning physiology at the level of the cell, tissue, organ and system.

Einstein said, "Everything should be made as simple as possible, but not simpler." That approach guides the ensuing discussion. We'll journey to some aspects of biology you may not have contemplated since your early collegiate education. But we will do so in a results-oriented spirit that

Five Ways to Build Momentum in Wellness

Once optometrists recognize the value that wellness interventions could bring to their patients, they get excited. And then, perhaps, they get a little dismayed at the prospect of having to get up to speed on a vast sphere of health that most likely didn't get enough attention in optometry college. Rectifying this is the very purpose and mission of OWNS. Here are five ways to help get the skills and contacts you need.

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 Nutritionist 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 eye 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 American Optometric Association. Here are the 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. At current rates, the 18-credit program would cost $7,236 for members. See www.ocularnutritionsociety.org/become-a-cns for more.

demonstrates how you can use this knowledge to teach your patients how to improve and sustain healthier lives.

The information provided is not for the privileged few who already have joined OWNS. It is designed for mass appeal, recognizing the diverse backgrounds of our growing and evolving profession. For the laboratory oriented, we are going to describe tests that have been found to predict 92% of epigenetic disease risk. For those not so inclined, we are going to describe the basics of nutrition and dietary supplementation. In any event, the OWNS board believes that learning this material will result in better health care at a lower cost, with less suffering.

KEEP IT GOING

No single educational piece can include everything, especially for such an all-encompassing area of knowledge as 'wellness.' Once you have (pardon the pun) digested the material here, the next logical step is membership in the Ocular Wellness and Nutrition Society.

Within this guide, we are going to highlight ODs, MDs and PhDs who have addressed these issues at length during previous OWNS biannual continuing education day and weekend-long seminars. Readers inclined to learn more are encouraged to join the conversation—you can engage in dialog with board members and other like-minded experts and enthusiasts at an OWNS meeting,

Collectively, the OWNS board represents a broad swath of academic thought leaders and busy clinicians. We are in the process of identifying an OWNS faculty representative and rotating student at each optometry college committed to public health and the future of our profession. We are partnering with the AOSA in this effort.

We wish to help you overcome challenges, so you can then assist your family and patients. The OWNS board thanks you for the opportunity to share our perspective and wishes you the greatest success in your patient care efforts. ❍

1.Greenland P, Fuster V. Cardiovascular risk factor control for all, JAMA, 2017;318(2);130-1.

4. Join the Academy's Nutrition, Disease Prevention & Wellness 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 liasion

Optometrists currently in practice and those students now joining the ranks can both reach out to an OWNS representative at their local college of optometry. The society is in the process of appointing an OWNS liasion at each of the colleges to serve as a resource. Below are the individuals currently participating as of press time; check www.ocularnutritionsociety.org for updates as they become available.

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

Keeping Nutrition True to the Letter

Healthy eyes and bodies need essential vitamins and minerals. Here's your guide, from A to zinc.

BY STUART RICHER, OD, PhD

Our patients can create circumstances conducive to wellness by making proper vitamin and mineral intake a goal rather than an afterthought in their lives. 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 and diabetic retinopathy.

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. The guide below highlights just a few key concepts for each, out of a vast body of nutritional knowledge that all doctors would do well to understand more deeply. OWNS presents this material with an eye toward the vision and ocular significance of these nutrients.

VITAMIN A

This vital substance supports all five senses, with particular relevance to olfaction, hearing and night vision. There are three dietary forms: 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 oxidized to retinoic acid. Given its importance to ocular health, vitamin A was included in both the AREDS1 and AREDS2 studies.

Pearls:

• Beta carotene is an effective antioxidant, but not an appropriate source of vitamin A, as it does not readily covert to preformed vitamin A (retinol) in the older population as it does in younger people. However, beta carotene is safer as it doesn't convert to vitamin A if there are sufficient stores currently in the system.

• There is some concern over increased risk of cancer in smokers and those who ingest second-hand smoke. This may have more to do with the creation of an imbalanced fat-soluble vitamin competition interfering with the absorption of vitamin D3, lutein, zeaxanthin and related molecules.

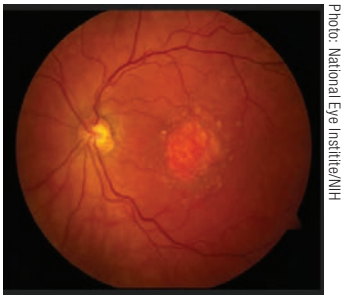


Photo: National Eye Institite/NIH

FIG. 1. Beta carotene, though an effective antioxidant, has been associated with elevated risk of AMD.

• In the Blue Mountains Eye Study, elevated beta carotene intake was associated with an increased risk of AMD.[1]

B VITAMINS

Prescribing this entire water-soluble synergistic family as a complex is the way forward, whether within a B50, B100, or better yet, within a comprehensive high-potency, multivitamin-mineral supplement. Here is a simplified rundown on these eight vitamins, letter by letter.

Vitamin B1 (thiamin). This underappreciated energy-producing vitamin is dramatically reduced in our American diet high in refined sugars, alcohol, coffee, tea and drugs that block its absorption. Thiamin 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. Thia-

min protects nerves, preventing the degeneration of myelin sheath coverings that manifests as neuropathy in patients suffering from alcohol and/or uncontrolled diabetes.

Pearl:

• Fat-soluble thiamin (benfo-thiamine) is an excellent supplement for our patients suffering from neuropathy, cardiomyopathy and what has been termed "Type 3 diabetes," i.e., Alzheimer's disease.

Vitamin B2 (riboflavin). As part of the cellular electron transport chain, riboflavin is another B vitamin needed 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 nonspecific and subtle. These include conjunctival injection, photosensitivity and dry eye. Dental manifestations include parched lips at the corners of the mouth and sore tongue. Skin manifestations include hair loss, acne and eczema. Neurologic manifestations include sleep loss, poor mental processing and neurodegenerative disease. Indeed, as with thiamin and other B vitamins, riboflavin contributes to overall health, wound healing, digestion, tissue growth and repair, fetal development and vitality. We need it.

Vitamin B3 (niacin) comes in three forms with different properties. It aids in the normal functioning of the human digestive system (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. Though nicotinic acid reduces high blood LDL cholesterol, and inositol hexaphopshate or IP6 is useful against cardiovascular disease and lowering blood pressure, the star form of this vitamin is niacinamide, which boosts mitochondrial function (and hence energy) known to be reduced in aging and neurodegenerative diseases such as Alzheimer's and Parkinson's.

Vitamin B5 (pantothenic acid) performs a wide variety of functions in our body. It aids in production of neurotransmitters and steroids, enhances immunity and liver detoxification, and assists in the extraction of fats, proteins and other vital nutrients from food. And it helps treat the chronic adrenal stress and anxiety of the American lifestyle. 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.

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

Vitamin B7 (biotin) is 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. Your patient experiencing dry scalp, dandruff or hair loss might be suffering from biotin deficiency.

Vitamin B9 (folate), the natural form of B9, is essential for the creation of DNA, preventing mutations and the growth of new cells. Specifically, folate plays a role in building new red blood cells, as well as 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 impressive health benefits of vitamin B9 include prevention of heart disorders, stroke, cancer and neural tube defects during early pregnancy. Folate also helps provides relief from mental and emotional disorders.

Folic acid is the synthetic version of vitamin B9 (pteroylmonoglutamic acid). It has historically been used as a supplement, but some 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, so there isn't an excess of undesirable partially metabolized or non-metabolized folic acid.

Brush Up On Your Chemistry 101

cofactor: Substance essential to the activity of the active ingredient.

covalent: Bond formed at the molecular level by the sharing of electrons.

divalent: Molecule having two chemical bonds.

isomer: Compound with the same formula as another but a different arrangement of atoms and, hence, different properties.

methylation: Chemical change to a protein that alters its function, e.g, to allow for detoxification, gene expression, immune response, energy production or other vital processes.

oxidation: The addition of oxygen to a molecule, e.g., during metabolization, creating free radical oxygen cells that contain unpaired electrons.

polyphenols: Micronutrients found in plant-based foods believed to have antioxidant properties and myriad other benefits.

redox: Short for reduction-oxidation reaction. A transfer of electrons in a chemical reaction that both increases (oxidizes) and decreases (reduces) the oxygen status. The process is essential to metabolic reactions.

Pearls:

• The folic acid found in most supplements is not metabolized in the digestive system, as folate is; rather, it must be moved to the liver, where multiple enzymatic reactions generate an active form. This slow multistep process results in high undesirable levels of non-metabolized serum folic acid and serum homocysteine (*see Biomarker 3, page 31*).

• Approximately 15% of people are under-methylators, impairing the conversion altogether. A 23andMe or similar genome-wide scan combined with "methylation" sub-analysis can clue the doctor in to this potential problem. Studies show that unmetabolized folic acid may have adverse 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) is cleaved from protein during digestion and therefore is dependent upon gastric intrinsic factor and parietal cell hydrochloric acid, both secreted by the stomach during digestion. As with food folate, cobalamin assists in cell maintenance and DNA formation. Vitamin B12 helps formation, repair and maintenance of red blood cells, providing relief for patients with pernicious anemia, megaloblastic anemia and sickle cell anemia.

Pearls:

• B12 supplementation often resolves symptoms of fatigue and neuritis (e.g., tingling, numbness) even when blood levels are adequate, indicating commonly occurring blood concentration is not adequate and therapeutic doses (i.e., above recommended daily allowance) are required.

• Vitamin B12 deficiency is rampant in Americans for at least three reasons: (1) as we age, hydrochloric acid secretion diminishes, leading to achlorhydria; (2) we routinely participate in chronic gastrointestinal acid blockade through the use of proton-pump inhibitors to treat acid reflux and other digestive issues; and (3) many individuals experience subclinical *H. pylori* infection, which interferes with absorption of cobalamin.

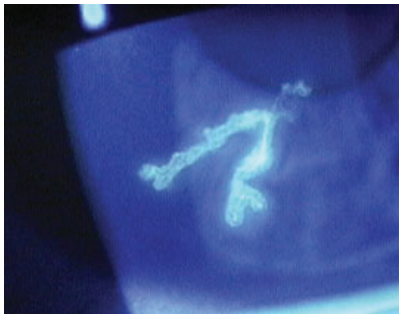


Photo: Aaron Bronner, OD

FIG. 2. Patients vulnerable to recurrent herpes simplex infection need to maintain vitamin D levels between 50ng/ml and 80ng/ml.

• Pernicious anemia is a common, often unrecognized disorder manifesting as lack of sensation in the hands and feet, low back pain, burning sensation of the tongue, loss of memory, poor coordination while walking, insomnia, drowsiness, constipation and headaches.

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 thrombocytopenia, important to those on anticoagulants.

Pearls:

• Incorrect dosing is common. Virtually no one except supplement users maintains 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.

• Sodium ascorbate is easier on the stomach than ascorbic acid. Note, however, this form's higher sodium level deems it inappropriate for some hypertensive patients.

• Overdose results in diarrhea and is used by clinicians to gauge prescriptive systemic requirements. Low vitamin C intake may contribute to development of silver wire arteriolar/hypertensive changes and severe arteriovenous nicking.

VITAMIN D3

This is really a hormone and one of the eight predictive biomarkers (*see page 32*), with some 73% of Americans insufficient or deficient. Besides absorption of calcium and phosphorous from the small intestine, this vitamin is involved in the modulation of more than 1,000 genes and plays a seminal role in the three top killers: cancer, cardiovascular disease and Alzheimer's. There are two forms: vitamin D2 (the less potent plant-based ergo-calciferol) and actual vitamin D3 (i.e., fish liver cholcalcefirol). Vitamin D3 converts into 1,25-hydroxy-cholciferol (calcitriol), the most potent endogenous steroid hormone. The most abundant source of vitamin D is sunlight.

The OWNS board reminds optometrists to proactively achieve a vitamin D status between 50ng/ml and 80ng/ml in our patients by calculating the required dose of D3 based on lab results. This is 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 systolic blood pressure, and the degree of arteriolar sclerotic retinopathy, arcus senilis and cardiovascular plaque.

Pearls:

• 25-hydroxy OH vitamin D serum liver reserve status varies by ethnicity, which is why it is critical to do this lab test or order a home finger blood spot test (see www.vitamindcouncil.org for testing kits) to calculate the proper dose. Unfortunately, the 25-OH D blood test is not yet part of routine blood screening but one's status correlates with morbidity and mortality.

• Vitamin D status is lower in people with higher melanin counts (i.e., darker skin) due to the pigment's interference with sunlight absorption. 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 AREDS1 and ARED2 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.

Pearl:

• A 2005 study in *JAMA* suggested that excessive (400 IU) vitamin E can be deadly! However, a closer look shows that the isolated finding applied only to an older cohort of patients (over age 70) with a long history of heart disease, stroke or diabetes, who were also taking a combination of medications, including ACE inhibitors, calcium channel blockers, anti-platelet agents and lipid-lowering agents during the course of the study. A significant number of subjects were also cigarette smokers.

ESSENTIAL MINERALS

In contrast to vitamins, which are large molecules, minerals are atoms and ions—right off the periodic chart *(Figure 4)*. Plants, bacteria and other microorganisms can't simply synthesize them. Your body cannot make these either, but 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, though a few minerals have been artificially re-introduced back into the soil.

Calcium is needed for muscle, heart and digestive cell messaging systems and is a constituent of bones and teeth.

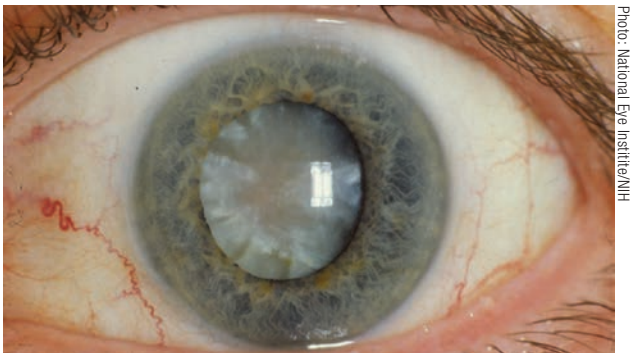


Photo: National Eye Institite/NIH

FIG. 3. The tocotrienols in vitamin E can retard cataract development.

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 a mineral 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, a forerunner to and fellow traveler in Type II diabetes.

Copper is necessary for the absorption and use of iron, and supports formation of hemoglobin and several enzymes, and is in fact a component of many enzymes, including cytochrome C oxidase. Labile copper is a strong divalent mineral that is 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. Almonds are a great dietary source. AMD eyes and Alzheimer's brains are over-mineralized with this divalent mineral.

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

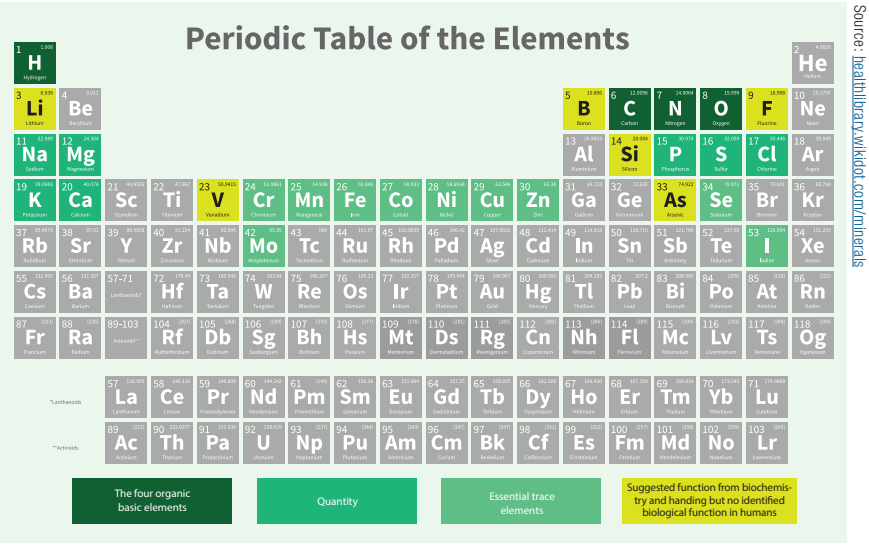
Iron. This divalent metal is part of the protein hemoglobin molecule that carries oxygen throughout the body. There are different intake requirements based on age (younger: important for growth) and gender (premenopausal: important due to blood loss).

KEEPING NUTRITION TRUE TO THE LETTER

Pearl:

• 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 (labile) and hence reactive oxidizing iron. AMD eyes are over-mineralized with divalent iron.

Magnesium (MG). The center atom of chlorophyll in dark green leafy vegetables, MG is the fourth most abundant mineral in the body and is involved in more than 300 biochemical reactions. MG supports bone mineralization, protein building, muscular contraction, nerve impulse transmission, immunity and mitochondrial adenosine triphosphate energy production. The 'forgotten anti-spasm mineral' is deficient, due to modern soil depletion and lack of intake of leafy vegetables in the American diet.



Source: healthlibrary.wikidot.com/minerals

FIG 4. Humans are now thought to require 60+ different "trace minerals" (shown in grey). These are found in root vegetables, fulvic-humic soil, ash and seaweed (kelp/dulce).

Pearls:

• Encourage supplementation or weekly Epsom salt baths/footbaths in addition to your patient's 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.

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

• In the past few decades, MG intake has dropped by 50% while the need for magnesium has increased by 50%.

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. The formation of cells, bones and teeth requires phosphorus, which also 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. Over-supplementation from food (i.e., vegetable juice, bananas) is to be avoided in severe chronic kidney disease. High serum potassium is mortal, as it can stop the heart.

Selenium. A cofactor essential to the activity of antioxidant enzymes like glutathione peroxidase, selenium 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 food such as garlic. It inhibits viral replication. Higher doses (i.e., 200mcg selenomethionine) 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. A cofactor of many enzymes and a transporter of vitamin A, zinc 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 the sclera, cornea, iris, lens, retina, choroid and optic nerve. Widespread worldwide deficiency is a more complex topic than currently appreciated. ❍

1. Tan JS, Wang JJ, Flood V, et al. Dietary antioxidants and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. Ophthalmology. 2008;115:334-341.

Carotenoids:
Essential to the Eyes—And More

Higher dietary intakes can improve ocular health, visual function and brain health and function.

BY LISA RENZI-HAMMOND, PhD, ELIZABETH JOHNSON, PhD, AND STUART RICHER, OD, PhD

Dietary lutein and zeaxanthin, produced naturally in red, yellow, orange and dark green fruits and vegetables, and meso-zeaxanthin, a metabolite of lutein, are important for a healthy retina. They aggregate in the macula more so than anywhere else in the body, and in the macula, 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 actinic (i.e., short-wave) light capable of damaging retinal tissue and by reducing inflammation.[5]

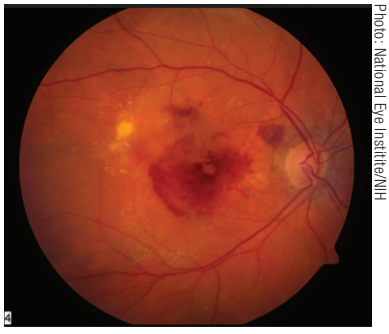


Photo: National Eye Institute/NIH

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

SHIELDS UP!

MP is thought to improve visual function primarily by absorbing short-wavelength light.[2] Exposure to damaging blue light (wavelength band of 435nm ±20nm) sets off a free radical chain reaction in ocular tissue, ultimately leading to oxidative stress and inflammation in the RPE.[5] Lutein and zeaxanthin, as both antioxidants and free-radical scavengers, filter light before it reaches the photoreceptors and RPE, staving off damage.[5] Such a protective role 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*).[3,6,7] For example, large cohort studies suggest that individuals with lower dietary levels of lutein and zeaxanthin in particular are at increased risk for developing AMD.[6-8] 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.[9] While most studies have focused on moderate and advanced AMD risk, carotenoids may also be beneficial for early disease.

The recent Central Retinal Enrichment Supplementation Trial 2 found antioxidant AREDS2 supplementation in patients with non-advanced AMD led to significant increases in macular pigment, as well as improved contrast sensitivity. AREDS2 suggests that antioxidant supplementation with lutein and zeaxanthin in the formulation can reduce risk of progression to late stages of AMD.[10]

While most of the research investigating the role of lutein and zeaxanthin in preventing AMD has focused on these carotenoids alone, lutein and zeaxanthin may also improve responses to standard treatments to wet AMD. For example, a recent two-year, randomized 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 without zeaxanthin. Adding oral zeaxanthin also led to a 74% reduced incidence of subsequent neovascular AMD in fellow eyes compared with eyes treated with triple therapy without zeaxanthin.[9] Supplementation may also lengthen the time between treatment cycles.[10]

CAROTENOIDS: ESSENTIAL TO THE EYE—AND MORE

Carotenoids Up Close

The color found in fruits, vegetables and flowers is at least in part because of the presence of carotenoids—pigments that enable many life-sustaining properties (e.g., photosynthesis) of these organisms. Over 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
- Beta-cryptoxanthin

Carotenes (primarily orange):

- Alpha-carotene
- Beta-carotene
- Lycopene

Depending on the country and culture, there are about 50 primary human dietary carotenoids available to human populations, 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 and zeaxanthin 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.

Cataracts. Carotenoids also play an important role in defusing accumulated superoxide radicals in the lens and protecting against cataracts.[11] 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.[12] This trend has been seen in other studies.[11]

Visual function. Short-wave light is particularly prone to intraocular scatter, which can cause glare and reduce visibility.[12] A number of studies suggest that by absorbing short-wave light, MP can improve a number of visual functions. For example, higher MPOP is associated with reduced glare disability, reduced photostress recovery times, improved heterochromatic contrast sensitivity and improved temporal contrast sensitivity.[4,13-15]

Cognition. Lutein and zeaxanthin are also the dominant carotenoids in the neocortex of the primate brain, including humans.[16,17] Carotenoid concentrations in the brain tend to relate to concentrations in the neural retina.[18] Since MPOD can be measured non-invasively in humans, it may be possible to use MPOD as a biomarker of lutein and zeaxanthin in the rest of the cortex.[19]

A number of recent studies have attempted to determine what the role of lutein and zeaxanthin in the cortex might be. Lutein and zeaxanthin tend to be dominant in cortex across the lifespan, including in early life.[20] The brain seems to preferentially absorb lutein, in particular, as concentrations in cortex tend to be higher than dietary intakes would predict, even in infancy *(Figure 2)*.[20] Recent research suggests that binding proteins such as STARD3 might be responsible for that selective uptake.[21]

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.[22,23] Recent studies have found support in children, young adults and healthy older adults.[23-27] This may be a possible mechanism to explain the finding that higher MP levels are related to improved cognitive function across the lifespan.[28-32]

GO "ALL-IN" ON MACULAR PROTECTION

The threat to our eyes posed by blue light is omnipresent. The sun, modern indoor LED lighting and digital screens all emit "bad blue" radiation. Simply put, we are awash in energetic blue light. Such pervasive exposure requires our protective strategies to be equally robust. The ideal approach combines blue light filters both internal (i.e., carotenoids) and external (glasses) with avoidance of excess exposure:

- In recent years, ophthalmic lens manufacturers have embraced blue light protection with new spectacle products that block deleterious wavelengths. Sunglass manufacturers have also embraced their product's role in eye health with better blue-blocking technology.
- Dietary ocular carotenoids also protect against "bad blue" light while protecting the desirable circadian rhythms mediated by "good blue" light. Optometrists should be well-versed in healthy dietary habits and edu-

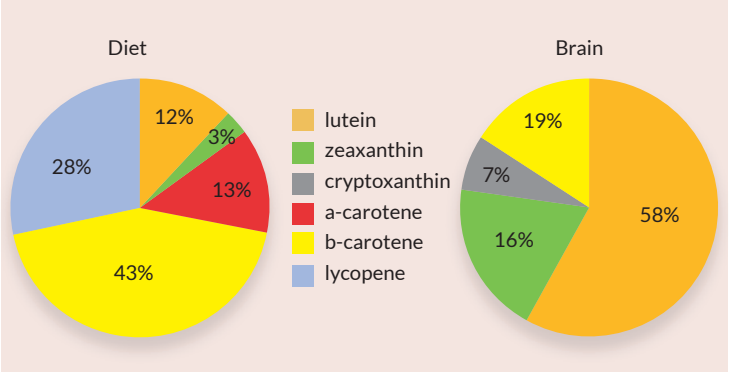


FIG. 2. Dietary intake vs. brain intake of carotenoids shows the brain's preferential absorption of lutein.[20]

Mind Your MPOD

MPOD can help shed light on a patient's relative risk of macular disease, considering research that shows an association between lower MPOD and an increased risk for AMD.[1,2] MPOD is a noninvasive metric determined with heterochromatic flicker photometry. It can also be measured over time, providing valuable information about therapeutic efficacy.

MP influences visual function through biological as well as optical mechanisms. The optical benefits include reduced glare disability and photophobia, two particularly common visual impairments. Higher MPOD is related to reduced glare disability, visual range and chromatic contrast.

Many Ocular Wellness and Nutrition Society members consider Snellen acuity and the Amsler grid to be useful, but not complete measures of visual function. Measuring MPOD, contrast sensitivity, glare disability and photostress recovery yield additional information about driving, sports and other ecological challenging activities.

1. Bernstein PS, Delori FC, Richer S, et al. The value of measurement of macular carotenoid pigment optical densities and distributions in age-related macular degeneration and other retinal disorders. Vision Research. 2010;50(7):716-28.

2. Richer S, Park D-W, Epstein R, et al. Macular re-pigmentation enhances driving vision in elderly adult males with macular degeneration, J Clin Exp Ophthalmology. 2012;3(3):1000217.

cate patients on how to make needed lifestyle changes. 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 for myriad health benefits. It is crucial to inquire if your patient regularly consumes dark green leafy vegetables (i.e. spinach, kale and collards). 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 supplements can add another layer of protection, particularly for at-risk patients. The indications for such interventions should be at the fingertips of every optometrist. According to Dr. Richer, patients already 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.[32-33] Patients taking warfarin are ideal candidates for carotenoid supplementation.

• 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." ❍

1. Bone RA, Landrum JT, Tarsis SL. Preliminary identification of the human macular pigment. Vision Res. 1985;25(11):1531-1535.
2. Snodderly DM, Handelman GJ, Adler AJ. Distribution of individual macular pigment carotenoids in central retina of macaque and squirrel monkeys. Invest Ophthalmol Vis Sci. 1991;32(2):268-279.
3. Ribaya-Mercado JD, Blumberg JB. Lutein and zeaxanthin and their potential roles in disease prevention. J Am Coll Nutr. 2004;23(6 Suppl):567S-587S.
4. Stringham JM, Hammond BR. Macular pigment and visual performance under glare conditions. Optom Vis Sci. 2008;85(2):82-88.
5. Yang JH, Basinger SF, Gross RL, Wu SM. Blue light-induced generation of reactive oxygen species in photoreceptor ellipsoids requires mitochondrial electron transport. Invest Ophthalmol Vis Sci. 2003;44(3):1312-9.
6. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Cochrane Database Syst Rev. July 2017.
7. Seddon JM, Ajani UA, Sperduto RD, et al. Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case-Control Study Group. JAMA. 1994;272(18):1413-1420.
8. Moeller SM, Parekh N, Tinker L, et al. Associations between intermediate age-related macular degeneration and lutein and zeaxanthin in the Carotenoids in Age-Related Eye Disease Study (CAREDS). Arch Ophthalmol. 2006;124(8):1151.
9. Renzi LM, Johnson EJ. Lutein and age-related ocular disorders in the older adult: A review. J Nutr Elder. 2007;26(3-4).
10. Chew EY, Clemons TE, Agrón E, et al. Effect of omega-3 fatty acids, lutein/zeaxanthin, or other nutrient supplementation on cognitive function. JAMA. 2015;314(8):791.
11. Weikel KA, Garber C, Baburins A, Taylor A. nutritional modulation of cataract. Nutr Rev. 2014;72(1):30-47.
12. Wooten BR, Hammond BR. Macular pigment: influences on visual acuity and visibility. Prog Retin Eye Res. 2002;21:225-240.
13. Hammond BR, Fletcher LM, Roos F, et al. A double-blind, placebo-controlled study on the effects of lutein and zeaxanthin on photostress recovery, glare disability, and chromatic contrast. Invest Ophthalmol Vis Sci. 2014;55(12):8583-89.
14. Renzi LM, Hammond Jr. BR. The relation between the macular carotenoids, lutein and zeaxanthin, and temporal vision. Ophthalmic Physiol Opt. 2010;30(4).
15. Renzi LM, Hammond BR. The effect of macular pigment on heterochromatic luminance contrast. Exp Eye Res. 2010;91(6):896-900.
16. Johnson EJ, Vishwanathan R, Johnson MA, et al. Relationship between serum and brain carotenoids, a-tocopherol, and retinol concentrations and cognitive performance in the oldest old from the Georgia centenarian study. J Aging Res. 2013;2013:951786.
17. Craft N, Dorey CK. Carotenoid, tocopherol, and retinal concentrations in elderly human brain. J Nutr Heal Aging. 2004;8(3):156-162.
18. Vishwanathan R, Schalch W, Johnson EJ. Macular pigment carotenoids in the retina and occipital cortex are related in humans. Nutr Neurosci. March 2015.
19. Wooten BR, Hammond BR, Land RI, Snodderly DM. A practical method for measuring macular pigment optical density. Investig Ophthalmol Vis Sci. 1999;40(11):2481-2489.
20. Vishwanathan R, Kuchan MJ, Sen S, Johnson EJ. Lutein and preterm infants with decreased concentrations of brain carotenoids. J Pediatr Gastroenterol Nutr. 2014;59;659-65.
21. Tanprasertsuk J, Li B, Bernstein PS, et al. Relationship between concentrations of lutein and StARD3 among pediatric and geriatric human brain tissue. PLoS One. 2016;11(5):e0155488.
22. Hammond BR, Wooten BR. CFF thresholds: relation to macular pigment optical density. Ophthalmic Physiol Opt. 2005;25(4):315-319.
23. Bovier ER, Renzi LM, Hammond BR. A double-blind, placebo-controlled study on the effects of lutein and zeaxanthin on neural processing speed and efficiency. PLoS One. 2014;9(9):e108178.
24. Walk AM, Khan NA, Barnett SM, et al. From neuro-pigments to neural efficiency: The relationship between retinal carotenoids and behavioral and neuroelectric indices of cognitive control in childhood. Int J Psychophysiol. 2017;118:1-8.
25. Mewborn CM, Terry DP, Renzi-Hammond LM, et al. Relation of retinal and serum lutein and zeaxanthin to white matter integrity in older adults: a diffusion tensor imaging study. Arch Clin Neuropsychol. November 2017:1-14.
26. Lindbergh CA, Renzi-Hammond LM, Hammond BR, et al. Lutein and zeaxanthin influence brain function in older adults: a randomized controlled trial. J Int Neuropsychol Soc. 2017 July:1-14.
27. Walk AM, Edwards CG, Baumgartner NW, et al. The Role of Retinal Carotenoids and Age on Neuroelectric Indices of Attentional Control among Early to Middle-Aged Adults. Front Aging Neurosci. 2017;9:183.
28. Renzi-Hammond L, Bovier E, Fletcher L, et al. Effects of a lutein and zeaxanthin intervention on cognitive function: a randomized, double-Masked, placebo-controlled trial of younger healthy adults. Nutrients. 2017;9(11):1246.
29. Johnson E, Vishwanathan R, Mohn E, et al. Avocado consumption increases neural lutein and improves cognitive function. FASEB J. 2015;29(Supp 1):32.8.
30. Hammond BR, Miller LS, Bello MO, et al. Effects of lutein/zeaxanthin supplementation on the cognitive function of community dwelling older adults: A randomized, double-masked, placebo-controlled trial. Front Aging Neurosci. 2017;9:254.
31. Barnett SM, Khan NA, Walk AM, et al. Macular pigment optical density is positively associated with academic performance among preadolescent children. Nutr Neurosci. May 2017:1-9.
32. Renzi LM, Dengler MJ, Puente A, et al. Relationships between macular pigment optical density and cognitive function in unimpaired and mildly cognitively impaired older adults. Neurobiol Aging. 2014;35(7).
33. Richer SP, Stiles W, Graham-Hoffman K, et al. Randomized, double-blind, placebo-controlled study of zeaxanthin and visual function in patients with atrophic age-related macular degeneration: the Zeaxanthin and Visual Function Study (ZVF) FDA IND #78, 973. Optometry. 2011;82(11):667-80.

DIET

Food for Thought:

How to Steer Patients Toward Healthier Habits

Food may act as medicine to promote wellness and minimize chronic disease, says the ophthalmologist who coined the word "superfood."

BY STEVEN G. PRATT, MD

At least three times a day we have the opportunity to influence our health through the dietary choices we make. Most of us have been conditioned to believe that unhealthy foods—those high in fat, sugar, salt and carbohydrates—taste better than healthy options. This notion, fostered at a young age, moves us away from habits that influence our general well-being, as well as our eye health and vision. We then spend much of our adult lives undoing the damage.

The genesis of my interest in preventing disease started with my mother. Mom was always reading *Prevention* magazine and quoting healthy tips from Adel Davis and Rachel Carson. Needless to say, our yard was organic. We grew oranges, lemons, tangerines, avocados, pineapple guavas and more. My mother had a natural cure for everything, and food was her preferred medicine. She passed away at age 91. Her death certificate stated she "died of old age."

Now, as a practicing ophthalmologist/oculoplastic surgeon in La Jolla, Calif., greatly influenced by these early life lessons, I have combined my passion for wellness with my interest in eye care. I have spent decades researching how foods and supplementation can benefit my patients' eye health by helping them optimize their overall and systemic well-being to potentially prevent age-related problems such as cataracts and macular degeneration.

A SUPERFOOD IS BORN

Believe it or not, I like to think I helped establish the term "superfood" in the collective consciousness of progressive medical and wellness communities almost two decades ago. A few years before my first book was published, my late agent suggested I write about food as medicine. Shortly after, while I was writing a prescription for a postoperative patient, the title "superfood" came to me. After a brief literature review, I decided to focus on superstar foods dense with nutrients associated with a long, healthy life. Around the same time, my colleague and coauthor, Kathy Matthews, coined the word "sidekick," which in this context means an alternate food that can be substituted in the same general category as a superfood.

To qualify as a superfood, something has to be readily available and have a significant number of scientific publications verifying the "power" of the food and its nutrients

A Deeper Dive

The guidelines I've provided in this article merely scratch the surface of proper nutrition habits. These concepts are developed extensively in the five books I've written on the topic:

- *SuperFoods Rx: Fourteen Foods That Will Change Your Life.* Pratt S, Matthews K. (2004). New York: William Morrow, an imprint of HarperCollins Publishers.
- *SuperFoods HealthStyle: Proven Strategies for Lifelong Health.* Pratt S, Matthews K. (2006). New York: William Morrow, an imprint of HarperCollins Publishers.
- *The SuperFoods Rx Diet: Lose Weight with the Power of SuperNutrients.* Bazilian W, Pratt S, Matthews K. (2008). New York: Rodale Inc.
- *SuperHealth: 6 simple steps, 6 easy weeks, 1 longer, healthier life.* Pratt S, Kolberg S. (2009). New York: Dutton (a division of Penguin Group).
- *SuperFoods Rx for Pregnancy: The Right Choices For A Healthy, Smart, Super Baby.* Pratt S. (2013). New Jersey: John Wiley & Sons.

Monitor Mercury Consumption While Getting Your Omegas

Mercury accumulates in streams and oceans and is converted to methylmercury in the water, which is then consumed by fish. This type of mercury can be harmful to unborn babies and young children; it has the potential to cause mental retardation, seizures, cerebral palsy, abnormal gait and/or speech and problems in vision and hearing. As such, women of reproductive age need to be especially careful about their fish intake. In addition, parents should be prudent with dietary choices for children. Tips to ensure minimal levels of mercury are consumed include:

- **Choose fish and shellfish known to be lower in mercury.** Five of the most commonly eaten seafood low in mercury are canned light tuna, wild salmon, shrimp and farmed tilapia and catfish.
- **Get more selenium in your diet.** Selenium is a protector against mercury toxicity.
- **Monitor your sushi consumption.** Pricier tuna tends to contain more mercury because it often derives from larger species that accumulate mercury from the fish they eat.
- **Don't eat shark, swordfish, king mackerel or tilefish.** They contain high levels of mercury.

to prevent disease and promote wellness and longevity. What follows are some of the pearls I have learned along the way and published in five books, starting in 2004.

FOODS TO PRESERVE EYESIGHT

The same antioxidant and anti-inflammatory containing nutrients that keep our heart and lungs healthy into our senior years also protect vision and hearing and keep our brains sharp. There is a direct relationship between the health of your senses and the soundness of your body. For example, studies have shown that people who have cataracts and macular degeneration also have a higher incidence of cardiovascular disease and premature death.

Generally speaking, nutrition is the cornerstone of good health. It helps to safeguard your vision and senses and aids in peak brain function. In particular, superfood nutrients mitigate many of the age-related changes our eyesight and brain experience during the maturing process. Here are foods loaded with superfood nutrients to do just that, recommended amounts and any associated sidekicks.

Pomegranates: Recommended amounts: 1/2 cup to one cup of 100% pomegranate juice, five to seven days

A 21st Century Solution to Fatigue: Increase Polyphenol Intake

Low energy and chronic fatigue are often warning signs of more serious disease. Most of us think this problem can be thwarted with the power of caffeine. Yet overreliance on coffee has its drawbacks, such as chronic depletion of thiamin (vitamin B1), whose deficiency negatively impacts every system of the body; coffee can also disrupt circadian rhythms.

While dangerously low energy is bad, natural sustained energy is desirable. The way our ancestors achieved this was by eating berries. These "superfoods" burn fat, are easy to digest and have a dramatic impact on improving endothelial function. They do this by improving metabolism and regulating sugar, decreasing inflammation and decreasing LDL (bad) cholesterol while raising HDL (good) cholesterol. In so doing, the antioxidant protective status of the body is raised.

Polyphenols are also the fuel for good bacteria (probiotics) and improve digestive comfort by decreasing dyspepsia (gas, bloating, diarrhea and constipation). After a meal, reach for the mixed berries (i.e., blueberries, strawberries, cherries and/or exotic cherry extracts of mulberry, berberine, pomegranate) and not typical carbohydrate- and fat-laden desserts. Green tea, cocoa and that glass of red wine are other great sources of polyphenols.

FOOD FOR THOUGHT: HOW TO STEER PATIENTS TOWARD HEALTHIER HABITS

a week. Pomegranate juice has been found to 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 giants. Many people aren't aware that these fruits have two to three times the antioxidant power of green tea or red wine, and also possess potent anti-inflammatory chemicals.[2]

Walnuts: Recommended amount: one handful, five times a week. Sidekicks: almonds, pistachios, sesame seeds, peanuts, pumpkin and sunflower seeds, macadamia nuts, pecans, hazelnuts and cashews. Walnuts have a high concentration of omega-3 fats. Since our cell membranes are primarily made of fats, nutrients attempting to enter/exit cells must pass through their outer membranes. The

fluid and flexible characteristics of omega-3 fats maximize cells' abilities to absorb their nutrients and eliminate wastes. In addition, ALA and other polyphenols in walnuts act as antioxidants to block adverse cellular signals from free radical exposure that can, over time, 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 progression by more than 50%.[3] At the same time, high intake of animal fat and processed foods substantially increased the risk of AMD.

Spinach: Recommended amount: one cup steamed, or two cups raw, five to seven days a week. Sidekicks: kale, collard greens, Swiss chard, arugula, mustard and turnip greens, bok choy, romaine lettuce, seaweed and purslane. The carotenoids that produce the colors found in many fruits and vegetables are powerful antioxidants that fight free radicals and act as anti-inflammatories, helping to reduce the risk of cataracts and macular degeneration. In particular the lutein and zeaxanthin found in spinach (as well as other green leafy vegetables and orange peppers) offer a notable risk reduction. The Nurses' Health Study shows that these carotenoids are the greatest deterrents to cataracts; participants who consumed raw or cooked spinach at least twice a week lowered their risk by 30% to 38% compared with those who consumed spinach less than once a month.[4]

Top Food Sources of Antioxidants

- ***Berries:*** blueberries, blackberries, raspberries, strawberries, acai and cranberries.
- ***Beans:*** small red and kidney beans, pinto and black beans.
- ***Fruits:*** many apple varieties (with the peel left on), avocados, cherries, green and red pears, fresh or dried plums, pineapple, oranges and kiwi.
- ***Vegetables:*** artichokes, spinach, red cabbage, red and white potatoes (with peel), sweet potatoes and broccoli.
- ***Beverages:*** green tea, coffee, red wine and some fruit juices.
- ***Nuts:*** walnuts, pistachios, pecans, hazelnuts and almonds.
- ***Grains:*** whole grain-based products
- ***Dessert:*** dark chocolate

Kiwis: Recommended amount: multiple times a week. Sidekicks: Brazilian, pineapple and strawberry guavas. 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. Recommended amount: one medium orange; 1/2 cup orange juice daily. Sidekicks: lemons, white and pink grapefruits, kumquats, tangerines and limes. Oranges are naturally rich in folate, a B vitamin.

Folate facilitates the processing of the amino acid homocysteine, which, when elevated, promotes atherosclerosis and inflammation. High homocysteine levels have been linked to increased risk for macular degeneration and cardiovascular disease and may be associated with increased risk of dementia and Alzheimer's disease.[5-8] Food folate along with vitamins B6 and B12 work together to lower

homocysteine levels and oxidative stress. Folic acid is the synthetic (non-superior) form of food folate, which in high doses may be problematic for genetic 'undermethylators' in the population.[9]

Choline and Betaine: On a related note, 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, brussel sprouts, broccoli and kidney beans. Good sources of betaine include wheat bran, quinoa, beets and spinach.

ANTI-INFLAMMATORY FOODS

Avoiding inflammation is key to maintaining vision health, since ongoing 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.[10]

As such, inclusion of anti-inflammatory foods is mission critical. Standouts in this category 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, don't forget to include free-radical-fighting foods such as blueberries and sidekicks purple grapes, cranberries, boysenberries, raspberries and strawberries; pomegranates and sidekicks plums and extra virgin olive oil, as well as nearly every spice.

Top Food Sources of Antioxidants

Without question, the carotenoids lutein and zeaxanthin are supernutrients for eye health.[1] So it's important to dose up daily on these esteemed nutrients.

- ***Good sources of lutein:*** Green leafy vegetables, including spinach, kale, collard greens, Swiss chard, arugula, mustard and turnip greens, bok choy, romaine lettuce, seaweed and purslane. Of these, spinach is king.
- ***Good sources of zeaxanthin:*** Orange bell peppers, goji berries, yellow corn and cornmeal are where you can find this illustrious nutrient.

1. The Age-Related Eye Disease Study 2 (AREDS2) Research Group. Lutein/Zeaxanthin for the treatment of age-related cataract: AREDS2 randomized trial report No. 4. JAMA Ophthalmol. 2013 May 5:1-7.

Daily Supplements

In an ideal world, we would get all the nutrients we need from food every day. However, the realities of modern life don't always make that a possibility. As a result, I recommend taking these supplements every day:

- **Multivitamins** that contain at least the following:
- **Lutein**
- **Zeaxanthin**
- **Alpha-lipoic acid**
- **Zinc with copper**
- **Vitamin C**
- **Vitamin E (full spectrum)**
- **EPA/DHA** (500mg to 1,000mg/day for adult women and 1,000mg to 2,000mg/day for adult men)
- **Vitamin D** (600 to 2,000 IU of D3 daily) for Caucasians, likely higher for darker-skinned patients

FUTURE CHOICES

We hold a great deal of power in our hands to influence our patients' choices in the medical realm. In the same vein, we can seize the opportunity to positively impact our patients' eye wellness and overall health from a preventive standpoint. As Thomas Edison said more than 100 years ago, "the doctor of the future will give no medicine but will interest his patients in the care of the human frame, in diet and in the cause and prevention of disease." ❍

1.Clemons TE, Kurinij N, AREDS Research Group. Associations of mortality with ocular disorders and an intervention of high-dose antioxidants and zinc in the Age-Related Eye Disease Study: AREDS Report No. 13. Arch Ophthalmol. 2004 May;122(5):716-26.

2.Gil MI, Tomás-Barberán FA, Hess-Pierce B, et al. Antioxidant activity of pomegranate juice and its relationship with phenolic composition and processing. J Agric Food Chem. 2000 Oct;48(10):4581-9.

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 Dec;121(12):1728-37.

4.Chasan-Taber L, Willett WC, Seddon JM, et al. A prospective study of carotenoid and vitamin A intakes and risk of cataract extraction in US women. Am J Clin Nutr. 1999 Oct;70(4):509-16.

5. Huang P, Wang F, Sah BK, et al. Homocysteine and the risk of age-related macular degeneration: a systematic review and meta-analysis. Sci Rep. 2015 Jul 21;5:10585.

6. Ganguly P, Fatima Alam S. Role of homocysteine in the development of cardiovascular disease. Nutr J. 2015;14:6.

7. Clarke R. B-vitamins and prevention of dementia. Proc Nutr Soc. 2008 Feb;67(1):75-81.

8. Luchsinger JA, Tang MX, Miller J, et al. Relation of higher folate intake to lower risk of Alzheimer disease in the elderly. Arch Neurol. 2007 Jan;64(1):86-92.

9. Lynch B, Dirty genes: a breakthrough program to treat the root cause of illness and optimize your health. HarperCollins, New York, NY, Harper One 2018.

10.Nelson JD, Craig, JP, Esen A, et al. TFOS DEWS II Report. Ocul Surf 2017; 2017 July;15(3):269-650.

The Science of Supplements

These products may help promote healthy eyes and vision when good eating habits aren't enough.

BY THE OWNS BOARD

One could easily assume that most Americans don't eat enough vegetables, fruits and other nutrient-rich foods, given the current rates 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' body mass index measurements, but they can be harmful to the eyes, vision, cognition and other critical systems in the body. The lack of proper nutrients creates a plethora of degenerative conditions and disease states throughout the body.

Even those who pride themselves on regularly eating healthy may not be getting optimal amounts of certain vitamins and nutrients that promote and maintain healthy vision and overall wellness for the long haul. Add to that increasing environmental toxins and blue light exposure from pervasive digital device usage and it's clear that many people may be coming up nutritionally short.

As a result, it has become essential for eye care patients, and people in general, to supplement their daily food intake with specific vitamins and nutrients. This can help safeguard against progressive damage from age-related diseases such as macular degeneration and cataracts, to preserve and enhance vision and all-around health for a lifetime.

AREDS & AREDS2 EYE SUPPLEMENTS

It's impossible to discuss eye supplementation without mentioning the Age-Related Eye Disease Study (AREDS) and its successor AREDS2, These two influential multicenter clinical trials on eye supplementation, sponsored by the National Eye Institute (NEI), followed thousands of participants for at least five years. The results showed benefits to using certain supplements to slow the effects of age-related macular degeneration (AMD).

AREDS, a randomized, placebo-controlled, double-masked clinical trial, investigated the impacts of a daily multivitamin supplement on the development and progression of AMD and cataracts in 4,757 participants, 55 to 80 years old.[2,3] Most participants had early or intermediate AMD at the time of enrollment, and the average follow-up period of the study was 6.5 years.

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.

Table 1. Major Eye Supplements on the Market Today

Manufacturer	Brand Names	For More Information
Alcon	• Systane ICaps AREDS Formula • Systane ICaps AREDS 2 Formula • Systane ICaps Multivitamin Formula • Systane ICaps Vision Health Formula • Systane ICaps Lutein & Zeaxanthin Formula	www.systane.com/products/eye-care
Bausch + Lomb	• Ocuvite Adult 50+ • Ocuvite Blue Light • Ocuvite Eye Health • Ocuvite Eye Health Gummies • Ocuvite Eye + Multi • Ocuvite Lutein • Ocuvite Lutein & Zeaxanthin • Ocuvite Lutein 25	www.ocuvite.com/family-of-products
Bausch + Lomb	• PreserVision AREDS Formula • PreserVision AREDS Lutein Formula • PreserVision AREDS 2 Formula • PreserVision AREDS 2 Formula + Multivitamin	www.preservision.com/products/preservision-eye-vitamins-overview
EyeScience	• Macular Health Formula • Dry Eye Formula • Computer Vision Formula • Premium Omega-3 Fish Oil	www.eyescience.com
Fortifeye Vitamins	• Fortifeye Complete Once Daily • Fortifeye Super Omega-3 Fish Oil • Fortifeye Super Protein • Fortifeye Focus	www.fortifeye.com
MacuHealth	• MacuHealth with LMZ3 • MacuHealth Plus	www.macuhealth.com
Nordic Naturals	• Omega Vision	www.nordicnaturals.com/consumers/omega-vision
PRN	• Dry Eye Omega Benefits • Nuretin • Eye Omega Advantage • Macular Vitamin Benefits	prnomegahealth.com
ScienceBased Health	• HydroEye • MacularProtect Complete AREDS2 • MacularProtect AREDS2 • DiaVis • OcularEssentials • OcularProtect • Optic Nerve Formula • OmegaAdvance	www.sciencebasedhealth.com/categorylist.aspx
TheraTears	• Eye Nutrition	www.theratears.com/products
ZeaVision	• EyePromise Restore • EyePromise EZ Tears • EyePromise Zeaxanthin + Lutein • EyePromise DVS • EyePromise AREDS 2 Plus Zinc Free • EyePromise AREDS 2 Plus Multivitamin • EyePromise Visual Edge • EyePromise Zeaxanthin • EyePromise Visual Edge Pro	www.eyepromise.com/products

AREDS Supplement Formulation

Very little major research has been funded on preventing early AMD. The AREDS formulations may delay progression of advanced AMD and help individuals preserve their vision longer if they have intermediate or advanced AMD in one eye.[1] Participants in the AREDS trial have been followed for at least 10 years, and the benefits of the AREDS formulation, comprised of AREDS and AREDS2 research, have persisted over this time.[1] The formulation is as follows:

- Vitamin C (500mg)
- Vitamin E (400IU)
- Zinc as zinc oxide (80mg)
- Copper as cupric oxide (2mg)
- Lutein (10mg)
- Zeaxanthin (2mg)

1. National Eye Institute. For the Public: What the AREDS Means for You. Available at: nei.nih.gov/areds2/patientfaq

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; copper was added to zinc-containing formulations to prevent copper deficiency, which may be associated with high levels of zinc supplementation).

Published in 2001, AREDS 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.[4] Within the high-risk group—individuals with intermediate AMD, or advanced AMD in one eye but not the other eye—the supplements reduced the risk of advanced AMD-triggered 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. These two adverse effects were addressed in the successor to AREDS.

AREDS2. In 2006, the NEI launched AREDS2, a five-year study 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.[5,6] Researchers chose to add the new carotenoids, which were in the same family as beta-carotene, 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.

More than 4,000 people ages 50 to 85 at risk for advanced AMD participated. They 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 combinations, including lutein/zeaxanthin (10mg/2mg), omega-3 fatty acids (1,000mg), lutein/zeaxanthin and omega-3 fatty acids, or placebo. Progression to advanced AMD was established by retinal photographs or treatment.

The study, completed in May 2013, 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.[7]

In addition, Dr. Chew said that long-term use of AREDS supplements appeared to be safe and protective against advanced AMD.[7] 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. Dr. Chew added that omega-3 fatty acids and beta-carotene didn't reduce the risk of progression to advanced AMD; however, adding lutein and zeaxanthin in place of beta-carotene might improve the formulation.

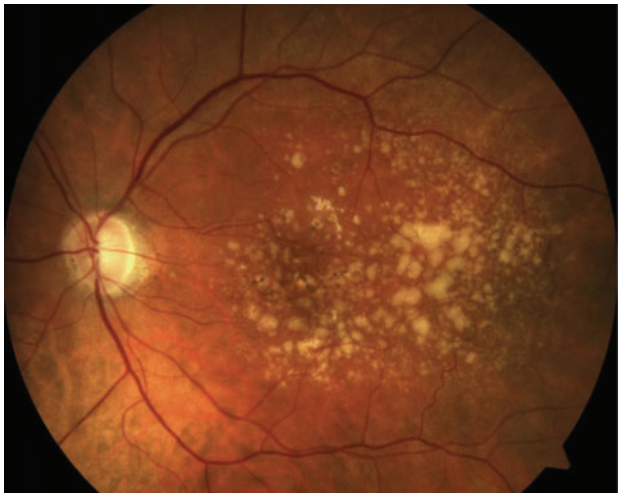


Photo: Andrew J. Rixon, OD

FIG. 1. The original AREDS study, released in 2001, found that AMD patients at high risk of disease progression reduced their risk by 25% after daily use of vitamins C and E, beta-carotene and zinc.

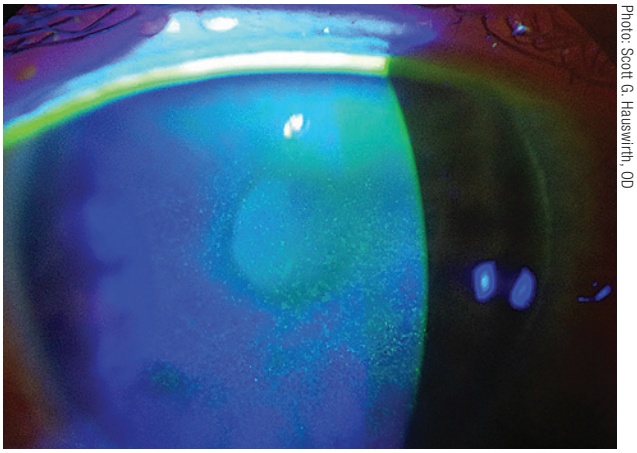


Photo: Scott G. Hauswirth, OD

FIG. 2. Omega-3 supplementation has long been used to help manage dry eye, but the recent DREAM study calls into question this practice. Experts dispute the findings, however.

DREAM STUDY & OMEGA-3 SUPPLEMENTATION

Despite the findings of numerous studies over the years touting the ocular health benefits of omega-3 supplementation, as well as the positive reports of many eye care professionals through the years, 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.[8]

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. The mean change in Ocular Surface Disease Index (OSDI) score was measured at six and 12 months; also monitored were mean changes in conjunctival staining score, corneal staining score, tear film break-up time (TBUT) and Schirmer's test score to assess supplement efficacy.

After one year of supplementation, the mean OSDI 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, TBUT and Schirmer's test score between the groups.

The findings initially caused quite a buzz in the optometric and ophthalmic communities, with some critics taking issue with the methodology of the study while other eye care professionals supported the validity of the study, and still others vowed to keep using omega-3 supplementation due to conflicting research and their own positive clinical experiences.

Daily Supplementation: Guidance from NHANES

A number of studies have provided guidance on daily supplements to promote eye health. The following recommendations for men and women over the age of 50 are based on the findings of the 2009-10 National Health and Nutrition Examination Survey.[1,2]

- Vitamin C (men: 90 mg; women; 75)
- Vitamin E as α-tocopherol (men: 15mg; women: 15mg)
- ß-carotene (men: 3mg to 6mg; women: 3mg to 6mg)
- Zinc (men: 11mg; women: 8mg)
- Lutein (men: 6mg; women: 6mg)
- Zeaxanthin (men: 6mg; women: 6mg)
- EPA/DHA (men: 250mg to 1,000mg; women: 250mg to 1,000mg)

1. Centers for Disease Control and Prevention National Health and Nutrition Examination SurveyAvailable from: http://www.cdc.gov/nchs/nhanes.htm (last accessed Aug. 16, 2018).
2. Rasmussen HM, Johnson EJ. Nutrients for the aging eye. Clin Interv Aging. 2013;8:741-8.

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, and then make educated decisions on how to proceed as clinicians. At the end of the day, we are accountable to our patients, and our decisions may come down to a combination of clinical experience (comprised of equal parts science and art), the unique needs of each patient and, ultimately, our own clinical instincts. 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. ❍

1. CDC National Center for Health Statistics. Prevalence of Obesity Among Adults and Youth: United States, 2015–2016. Available at: https://www.cdc.gov/nchs/data/databriefs/db288.pdf (last accessed Aug. 16. 2018).

2. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. ArcArch Ophthalmol. 2001;119(10):1417-36.

3. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. Arch Ophthalmol. 2001;119(10):1439-52.

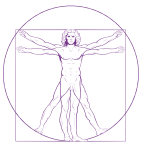
4. National Eye Institute. Antioxidant Vitamins and Zinc Reduce Risk of Vision Loss from Age-Related Macular Degeneration. Available at: https://nei.nih.gov/news/pressreleases/101201 (last accessed Aug. 16, 2018).

5. AREDS2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial.. 2013 May 15;309(19):2005-15.

6. AREDS2 Research Group. Lutein/Zeaxanthin for the Treatment of Age-Related Cataract AREDS2 Randomized Trial Report No. 4. JAMA Ophthalmol. 2013;131(7):843-50.

7. National Eye Institute. NIH study provides clarity on supplements for protection against blinding eye disease. Available at: https://www.nei.nih.gov/news/pressreleases/050513 (last accessed Aug. 16, 2018).

8. Dry Eye Assessment and Management Study Research Group. n-3 Fatty Acid Supplementation for the Treatment of Dry Eye Disease. N Engl J Med. 2018 May 3;378(18):1681-90.



Four Great Debates in Ocular Nutrition

Where do you stand on these controversies?

BY DENNIS RUSKIN, OD, JULIE POTEET, OD, CNS, AND STUART RICHER, OD, PhD

One mark of a healthy field of study is the amount of discussion it generates. In that regard, ocular nutrition is fit as a fiddle! Experts have been debating some topics for decades, while others have come into the conversation just this year.

1 DOES GENETIC TESTING REVEAL VULNERABLILITY TO HIGH ZINC LEVELS?

Who could have guessed, back in 2001 when the Age-related Eye Disease Study (AREDS) was published, that the work would kick up a firestorm of controversy in the seemingly unrelated topic of genetic testing more than a decade later? At the center of the storm is a fundamental disagreement between the National Eye Institute's Emily Chew, MD, who ran the AREDS studies, and private practitioner Carl Awh, MD. Both are retina specialists.

A closer examination of the AREDS data by some investigators revealed a paradoxical effect in some subjects who worsened, causing an increase in choroidal neovascularization, while most subjects benefited. Zinc was implicated in the AREDS formulation as the culprit.

In 2013, Dr. Awh revealed that genetics, specifically the CFH and ARMS2 risk allele, could predict response to the AREDS formulation.[1] He showed that 13% of subjects in an AREDS dataset with CFH risk alleles had an increased risk for visual loss. In 2014, Dr. Chew released a rebuttal paper disputing the findings and asserting that the AREDS formulation was effective across all genotypes.[2] Both Drs. Chew and Awh went on the offense to criticize each other in letters to peer-reviewed journals and at professional meetings. Clinical investigators, statisticians and thought leaders have also weighed in on both sides.

Reviews of the scientific literature linking human biology to AREDS research have provided a further understanding concerning AREDS and the safety of supplemental zinc. In 2008, Klein et al. suggested that genetics might affect the AREDS formula's performance, particularly with subjects with high CFH risk alleles.[3] Also in 2008, Lengyel et al. reported that retinal drusen acted like amyloid deposits in aging eyes and were filled with anomalous deposits of zinc.[4] Ten years later, Assel et al. published a re-analysis of AREDS data asserting that AREDS was safe for all genotypes.[5] Drs. Chew, Awh and Assel studied the same clinical endpoint, i.e., subjects who had progressed to advanced

Zinc for Yourself

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.

1. Prasad AS. Trace Elements in Human Health & Disease, Volume I. Academic Press: London 1977.

Photo: Julie Poteet, OD

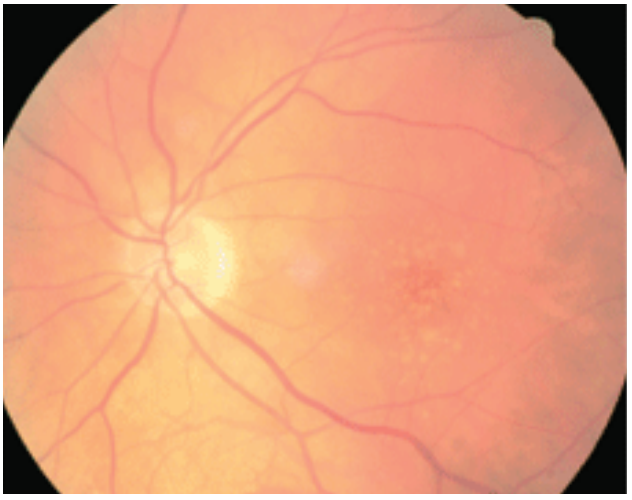


FIG. 1. This eye qualifies as intermediate AMD per the AREDS classification system. The patient would benefit from supplementation.

AMD, specifically choroidal neovascularization (CNV) or geographic atrophy (GA). However, we believe combining CNV and GA subjects obscured the results *(Figure 2)*.

Drs. Johanna Seddon and Demetrios Vavvas offered a different methodology and statistical analysis of AREDS data by focusing on subjects who only progressed to CNV. In 2016, Dr. Seddon demonstrated that genetic variation accounted for statistically significant differences in patient response.[6] She noted that one-third of subjects did worse but two-thirds did better, and in some cases experienced an ~85% reduction in CNV risk. In a re-analysis of AREDS data published in December 2017, Vavvas et al. included the largest cohort of subjects so far. The team concluded that CFH and ARMS2 risk alleles determined progression to CNV after antioxidant and zinc supplementation.[7]

In particular, the investigators found that patients with high-risk CFH and low-risk ARMS2 might be harmed by AREDS with a hazard ratio (HR) of 2.92 or a ~300% (p=0.018) increased risk of vision loss due to CNV. Other low-risk CFH and high-risk ARMS2 groups had a HR of 0.5 (p=0.008), suggesting AREDS was helpful. So AREDS worked for some but not others.

Fortunately, optometrists can now assess the risk of developing AMD based on factors including age, environment and genetics, as well as stage of the disease by examining a patient's fundus using ophthalmoscopy and OCT. CNV progression risk can be predicted using genetic testing, retinal appearance and assessment of lifestyle habits.

The legacy of AREDS is the study's role in determining how an 'average subject' would respond to a drug or intervention. However, each of us is not average due to our unique diet and genetics. Genetic testing is appropriate and reasonable, especially to optimally protect the remaining eye in monocular AMD.

2 MESO-ZEAXANTHIN: WHERE DO WE GO FROM HERE?

We would argue that the fovea is the most valuable real estate in the eye. With its tightly packed cones and two major retinal carotenoids (zeaxanthin and meso-zeaxanthin), it is critical for hyperacute visual acuity and color vision. Unfortunately, the fovea is also the most vulnerable area for occult subretinal neovascular membrane formation in AMD.

Though we disagree with the claim that supplementing with lutein, zeaxanthin and meso-zeaxanthin on a long-term basis is superior to supplementing with just lutein and zeaxanthin, we are encouraged by research on the short-term use of zeaxanthin and meso-zeaxanthin for late-stage AMD.

Let's start with the CREST2 trial, which evaluated the impact of supplementation with lutein, zeaxanthin and meso-zeaxanthin in early AMD.[8] The two-year, randomized, double-blind, controlled study compared a 25mg zinc/AREDS2 formulation vs. 25mg zinc/AREDS2 plus 10mg of meso-zeaxanthin in minimal-risk AMD patients. The primary outcome measure was letter contrast sensitivity (CS) at six cycles per degree. CREST 2 showed no difference in this primary outcome (p=0.88). Global improvement in CS and secondary measures of visual function were virtually identical with or without the addition of 10mg meso-zeaxanthin.

Of concern, the meso-zeaxanthin-enhanced formulation dramatically diminished serum zeaxanthin levels (p=0.005). This is troubling because dietary lutein and zeaxanthin have emerged as crucial brain nutrients. More work needs to be done to address the issue of carotenoid competition.

In another questionable finding for meso-zeaxanthin, a team of researchers looking at retinal proteins and carotenoids demonstrated that the isomerase enzyme RPE65 was responsible for converting lutein to meso-zeaxanthin in vertebrates.[9,10] This essentially implied that retinal meso-zeaxanthin was readily available to those supplementing with lutein.[11]

On a more positive note, two other published clinical studies investigating supplementation of zeaxanthin, and anecdotally meso-zeaxanthin, on approximately 700 patients resulted in fewer anti-vascular endothelial growth factor (VEGF) injections.[12-14] This reduced AMD progression in the fellow eye by 75%.[12,13]

In January 2018, retina specialist Michael Tolentino, MD, showed positive findings from case reports (n=38) of high-risk AMD patients co-treated with anti-VEGF agents,

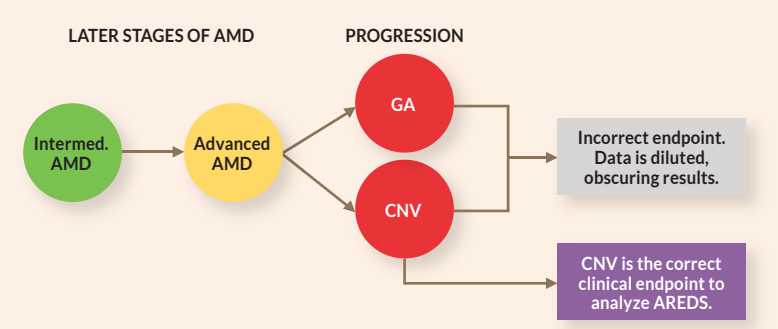


FIG. 2. Chew, Awh and Assel included subjects who progressed to both GA and CNV. Seddon and Vavvas restricted their analysis to subjects who progressed to CNV—the correct clinical endpoint.

and lutein, zeaxanthin and meso-zeaxanthin.[15] Further studies are needed to confirm the impact of such reports.

Supplementing with a zeaxanthin dose above the 2mg set forth in the AREDS2 formula, or consumption of orange peppers (rich in zeaxanthin), can build denser foveal macula pigment optical density. Some clinicians opt to recommend higher doses of lutein while others prescribe higher dosages of zeaxanthin beyond 2mg. Still other practitioners believe prescribing meso-zeaxanthin to build denser macular pigment is the way forward.

Post-AREDS science has not fully addressed foveal protection and adjunct anti-VEGF therapy with high-dose zeaxanthin, meso-zeaxanthin and lutein. Neither has it assessed the long-term effects of meso-zeaxanthin and potential depression of lutein and zeaxanthin.[16] Hopefully, the NEI will sort this all out in a well-controlled, carefully designed, post-AREDS2 high-dose zeaxanthin isomer study.

3 SHOULD YOU STOP RECOMMENDING FISH OIL SUPPLEMENTS IN THE WAKE OF THE DREAM STUDY?

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 (DED) patients compared with a placebo group taking olive oil.[17] The study is compelling in every respect except for its potentially poor choice of placebo.

The olive polyphenols found in healthy Mediterranean diets, i.e., hydroxytyrosol (an o-diphenol) have powerful anti-inflammatory, antioxidant and anti-thrombotic properties. A separate study in 2016 of olive oil consumption and AMD taught us that olive oil has potency against the disease.[18] After adjusting for potential confounders, Cougnard-Grégoire, et al. determined that regular use of olive oil was significantly associated with a decreased risk of late AMD (OR=0.84, 95% CI: 0.59;1.21). Perhaps findings such as these explain why the overall DREAM outcomes of the omega-3 and olive oil arms were positive.

It's possible that omega-3 supplementation and olive oil have a positive impact on the treatment of dry eye. In DREAM, most dry eye symptoms and signs appeared to improve in both arms, and a meaningful statistical change was detected between baseline and 12 months in the conjunctival, and corneal staining scores, and tear break-up time ($p<0.001$).

However, the DREAM research team has countered that the dose of the olive oil placebo (5,000mg), compared with that in a Mediterranean diet (60g), was too low to have had a therapeutic effect.[19] The team has also argued that the anti-inflammatory effects associated with olive oil are attributed mainly to polyphenols in extra virgin olive oil, not found in the refined olive oil used in the DREAM study. As well, the researchers have noted, the Mediterranean diet includes other key components beyond olive oil, such as nuts, fresh fruits, vegetables and fish.[20] Lastly, the DREAM research team has countered that the intake of olive oil in the DREAM placebos had a very low or no impact on systemic levels of oleic acid, the predominant component of olive oil—a 1% mean decrease from baseline in the placebo group when the level of oleic acid was measured in red blood cell membranes. This was in contrast to the mean increase of approximately 400% for eicosapentaenoic acid (EPA) and 40% for docosahexaenoic acid (DHA) in the group assigned to omega-3 supplements. Based on these facts, the DREAM team has concluded that it doesn't believe that one teaspoon of refined olive oil daily would exert a therapeutic effect on dry eye disease.

While the protective polyphenols of the olive oil were removed by the refining process, DREAM's argument that the anti-inflammatory effects of the placebo were removed does not take into account the effects of both oleic acid and linoleic acid upon the structure of the microbiome. While DREAM researchers showed that uptake of oleic acid into the bloodstream proved minor by testing, the local effects on gut tissue must be anticipated. Oleic acid has been shown to alter the microbiome and reduce dysbiosis, conferring anti-inflammatory effects elsewhere in the body. Oleic acid has also been shown to counter the negative impact of saturated fat on the microbiome.[21]

Understanding the biochemistry of fatty acid metabolism is imperative in the interpretation of the results of the study. It has been well documented that fatty acids compete for space in cellular membranes, and supplementation with a single fatty acid can exacerbate depletion of other fatty

acids. For example, supplementation with EPA and DHA reduces DGLA.[22] Some of the unique health-promoting effects of DGLA are nutrigenomic, mediated via activation of PPAR-gamma and the resultant inhibition of NFkB.[23] Therefore, a strong argument can be made that supplementation with high-dose fish oil should only be accompanied by the healthy omega-6 gamma linoleic acid (GLA) to obtain the maximum benefits and avoid depleting necessary GLA.

Given all this, as well as many prior studies and clinical reports indicating various therapeutic benefits to dry eye patients from proper omega-3 supplementation, the jury is still out on DREAM. So, let's not throw fish oil overboard yet, as it is a predictive biomarker of healthy aging. Not only does adding fish three times a week to the diet (7 ounces or more) offer the anti-inflammatory benefits of fish oil, it also provides protein, vitamins D, B2 and calcium. Despite all of the controversy surrounding omega-3 supplementation, we still believe omega-3—and its associated DHA—are all-star nutrients for retinal and brain health.

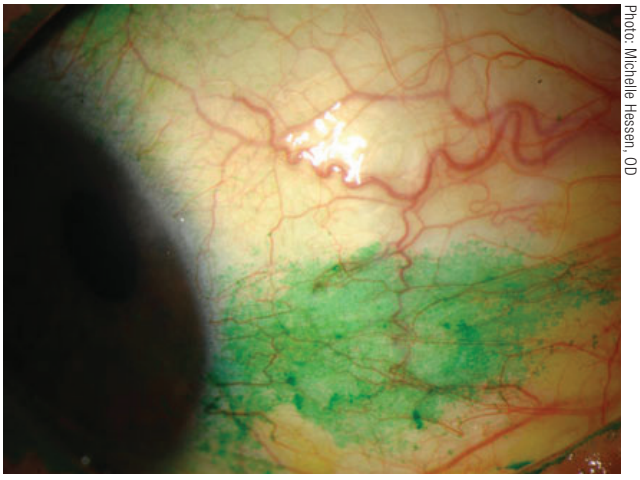


Photo: Michelle Hessen, OD

FIG. 3. Conjunctival staining in this dry eye patient would prompt many ODs to recommend fish oil. The DREAM study calls that practice into question.

4 IS RESVERATROL READY FOR PRIME TIME?

The potential is real for small molecular-weight-nutrient molecules resveratrol (RV), found in red wine, and the commercial product Longevinex to impact multisensory degenerations of aging (vision, cognition and hearing) through molecular medicine pathways.[24] RV reduces inflammation, inhibits VEGF gene expression, increases endogenous antioxidant enzyme activity, mimics caloric restriction along with offering numerous other health benefits—including enhancement of mitochondrial function—that decline with aging. RV notably inhibits all three stages of carcinogenesis: initiation, promotion and metastasis, with over 3,000 PubMed citations.

Other direct mitochondrial-enhancing nutrients include: nicotinamide, coenzyme Q10, pyrroloquinoline quinone, L-carnitine, lipoic acid and B vitamins.

The polyphenolic nutraceutical Longevinex and high-dose zeaxanthin resolve drusen and have elicited no reported safety concerns in more than a decade of human

Eights Threats to Counter

By Stuart Richer, OD, PhD

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 diffiult to effect change in mindset and behavior among some doctors, let alone patients.

1. Lectins
2. Soy products
3. Broad-spectrum antibiotics
4. NSAIDs
5. Gastrointestinal acid blockers
6. Artificial sweeteners
7. Hormone disruptors
8. Herbicides

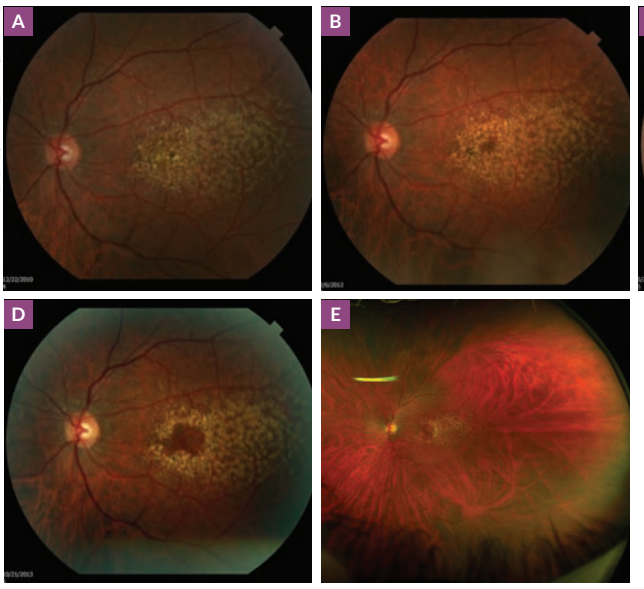
Two of these deserve extra attention:

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.

1. Gundry SR. The plant paradox: the hidden dangers in "healthy" foods that cause disease and weight gain. New York, New York: Harper Wave.



Photos: Stuart Richer, OD, PhD

FIG 4. This patient experienced partial clearing of foveal drusen, but no changes in Amsler grid or SD-OCT, while taking a statin (A, B). He then self-prescribed daily Longevinex supplementation. This combination approach resulted in additional clearing of foveal drusen (C). He eventually discontinued the statin, maintained Longevinex and began a calorie-restricted diet and an exercise regimen. The Amsler grid symptoms began to resolve and he experienced further reduction in drusen (D). As of his last retinal evaluation, he has remained free of visual defects on Amsler grid (E) with 20/20 vision.

use. In contradistinction, pharmaceutically invasive intravitreal anti-VEGF AMD injections have been shown to induce a 500% increase in destruction of the photoreceptor RPE complex, potentially resulting in eventual loss of vision.[25] Even the act of removing a cataract and implanting an intraocular lens can increase the risk of AMD 2.68-fold by five years after surgery.[26] After a stroke, mortality has been shown to increase sixfold following anti-VEGF therapy, suggesting that these now common treatments might have systemic effects that impair normal wound healing.[27,28]

Thus, there is an imperative to explore complementary adjunctive therapies in the hopes of sparing more patients from permanent blindness, death or the undesirable long term sequelae of traditional treatments. We believe that RV generally or Longevinex in particular, should be evaluated in large-scale studies alongside traditional therapeutic approaches. ❍

1. Awh C, Lane AM, Hawken S, et al. CFH and ARMS2 genetic polymorphisms predict response to antioxidants and zinc in patients with age-related macular degeneration; Ophthalmology. 2013 Nov;120(11):2317-23.
2. Chew EY, Klein ML, Clemons TE, et al. No clinically significant association between cfh and arms2 genotypes and response to nutritional supplements: AREDS Report Number 38. Ophthalmology. 2014 Nov; 121(11): 2173-80.
3. Klein ML, Francis PJ, Rosner B, et al. CFH and LOC3087715/ARMS2 genotypes and treatment with antioxidants and zinc for age- related macular degeneration. Ophthalmology. 2008 Jun;115(6):1019-25.
4. Lengyel I, Flinn JM, Peto T, et al. High concentration of zinc in sub-retinal pigment epithelial deposits. Exp Eye Res. 2007 Apr;84(4):772-80.
5. Assel MJ, Li F, Wang Y,et al. Genetic polymorphisms of CFH and ARMS2 do not predict response to antioxidants and zinc in patients with age-related macular degeneration: independent statistical evaluations of data from the age-related eye disease study. Ophthalmology. 2018 Mar;125(3):391-7.
6. Seddon JM, Silver RE, Rosner B. Response to AREDS supplements according to genetic factors: survival analysis approach using the eye as the unit of analysis. Br J Ophthalmol. 2016 Dec;100(12):1731-7.
7. Vavvas D, Small K, Awh C, et al. CFH and ARMS2 genetic risk determines progression to neovascular age-related macular degeneration after antioxidant and zinc supplementation. Proc Natl Acad Sci U S A. 2018 Jan 23;115(4):E696-704.
8. Akuffo KO, Beatty S, Peto T, et al. The impact of supplemental antioxidants on visual function in nonadvanced age-related macular degeneration: a head-to-head randomized clinical trial. Invest Ophthalmol Vis Sci. 2017;Oct 1;58(12):5347-60.
9. Shyam R, Vachali P, Gorusupudi A, et al. All three human scavenger receptor class B proteins can bind and transport all three macular xanthophyll carotenoids. Arch Biochem Biophys. 2017 Nov 15;634:21-8.
10. Shyam R, Gorusupudi A, Nelson K, et al. RPE65 has an additional function as the lutein to meso-zeaxanthin isomerase in the vertebrate eye. Proc Natl Acad Sci U S A. 2017 Oct 10;114(41):10882-7.
11. Shyam R, Gorusupudi A, Nelson K, et al. RPE65 has an additional function as the lutein to meso-zeaxanthin isomerase in the vertebrate eye. Proc Natl Acad Sci U S A. 2017; Oct 10;114(41):10882-7.
12. Olk RJ, Peralta E, Gierhart DL, et al. Combination therapy with dietary zeaxanthin for neovascular age-related macular degeneration. A randomized clinical trial. J Clin Exp Ophthalmol 2017 8(5):692.
13. Olk JR, Peralta E, Gierhart DL, et al. Triple combination therapy and zeaxanthin for the treatment of neovascular age-related macular degeneration: an interventional comparative study and cost- effectiveness analysis. Int J Retina Vitreous. 2015 Nov 9;1:22.
14. Tolentino M, MD. Northeast Chicago Optometric CE meeting, 2018; Jan 28.
15. Tolentino M. Nutrition & Disease Management. West Suburban Optometric Society Meeting & CE. 28 January 2018; Naperville, IL.
16. Vishwanathan R, Neuringer M, Snodderly DM, et al. Macular lutein and zeaxanthin are related to brain lutein and zeaxanthin in primates. Nutr Neurosci. 2013 Jan;16(1):21-9.
17. Dry Eye Assessment and Management Study Research Group. n-3 Fatty Acid Supplementation for the Treatment of Dry Eye Disease. N Engl J Med. 2018 May 3;378(18):1681-1690.
18. Cougnard-Grégoire A, Merle BM, Korobelnik JF, et al. Olive oil consumption and age-related macular degeneration: the alienor study. PLoS One. 2016 Jul 28;11(7):e0160240.
19. Gorzynik-Debicka M, Przychodzen P, Cappello F, et al. Potential Health Benefits of Olive Oil and Plant Polyphenols. Int J Mol Sci. 2018 Feb 28;19(3). pii: E686.
20. Estruch R, Ros E, Salas-Salvadó J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med. 2018 Jun 21;378(25):e34.
21. Alcock J, Lin H. Fatty acids from diet and microbiota regulate energy metabolism. Version 1. F1000Res. 2015; 4(F1000 Faculty Rev):738.
22. Cleland LG, Gibson RA, et al. The effect of dietary fish oil supplement upon the content of dihomo-gammalinolenic acid in human plasma phosholipids. Prostaglandins Leukot Essent Fatty Acids 1990 May;40(1):9-12
23. Vasquez A. Reducing pain and inflammation naturally, Part II: new insights into fatty acid supplementation and its effect on eicosanoid production and genetic expression. Nutritional Perspectives: J Counc Nutr Am Chiro Assoc. 2005;28(1):5-16.
24. Richer S, Ulanski L, Popenko NA, et al. Advances in Ophthalmology and Optometry: AMD beyond AREDS II. Yanoff M. ed. Philadelphia, Elsevier Press; 2016.
25. Sophie R, Wang J, Campochiaro PA. Re: Grunwald JE, Daniel E, Huang J, et al.: Risk of geographic atrophy in the comparison of age-related macular degeneration treatments trials (Ophthalmology 2014;121:150-61). Ophthalmol. 2014;121(7).
26. Ho J, Xirasagar, S, Kao L, et al. Neovascular age related macular degeneration is associated with cataract surgery. 2018 Mar;96(2):e213-e217.
27. Hanhart J, Comaneshter DS, Freier Dror Y, et al. Mortality in patients treated with intravitreal bevacizumab for age-related macular degeneration. BMC Ophthalmol. 2017 Oct 10;17(1):189.
28. Hanhart J, Comaneshter DS, Freier-Dror Y, et al. Mortality associated with bevacizumab intravitreal injections in age-related macular degeneration patients after acute myocardial infarct: a retrospective population-based survival analysis. Graefe's Archive for Clin and Exp Ophthalmol. April 2018; 256(4):651-63.

The Microbiome and Us: Partners for Life

Systemic and ocular microbial populations provide vital services to the body and eyes.

BY JULIE POTEET, OD, CNS, AND DOROTHY HITCHMOTH, OD

Over a hundred trillion bacteria live within us and on us. That's tenfold higher than the number of cells in the human body itself. With a collective weight of 1kg to 1.5kg, this microbiome can be considered an additional human 'organ' of sorts, rivaling the liver in the number of biochemical reactions in which it participates.

This entity contains about four million distinct bacterial genes, 95% or more located in the large intenstine, where they enhance gut motility and function. Colon bacterial species can be divided into potentially harmful or health-promoting groups. "Since most of these genes encode for enzymes and structural proteins that influence the functioning of the mammalian cells," a recent study notes, "the gut microbiome can be viewed as an anaerobic bioreactor programmed to synthesize molecules which direct the mammalian immune system, modify the mammalian epigenome, and regulate host metabolism."[1]

GUT INSTINCT

Microbiomes are clusters of mainly bacteria, as well as a few other organisms found in our mouth, skin, nose, urogenitals, ocular tissue and gut. In recent years, scientists have discovered that the gut microbiome orchestrates human metabolism, immunity and gene expression.

The gastrointestinal microbiome 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. A healthy gastrointestinal (GI) tract improves digestion and nutrient absorption (contributing approximately 10% of daily energy needs), salvages energy from unabsorbed carbohydrates in the colon to form short-chain fatty acids and improves the absorption of calcium, magnesium and trace minerals. A healthy GI tract also produces vitamins in the B and K groups. It also facilitates xenobiotic metabolism, important for the absorption and proper functioning of phytoestrogens, lignans, flavonoids and some medicinal herbs.

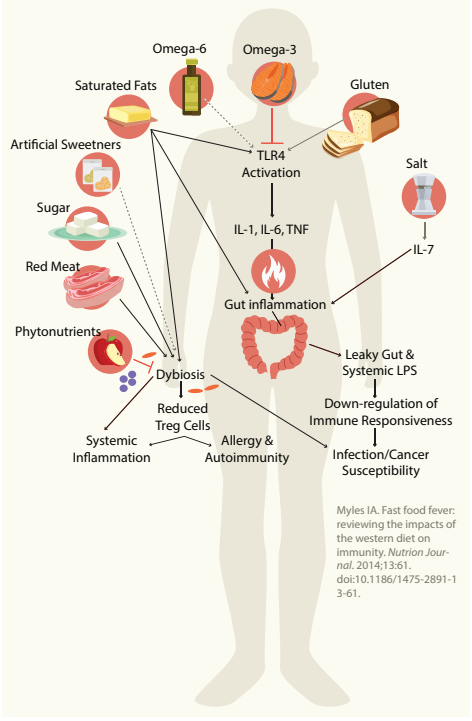


FIG. 1. In recent years, scientists have discovered that the gut microbiome orchestrates human metabolism, immunity and gene expression.

Dysbiosis is defined as qualitative and quantitative changes in the intestinal flora, their metabolic activities, or their local distribution that produces harmful effects on the host. Our modern diet and lifestyle, as well as the use of pharmaceutical drugs, has led to the disruption of the normal intestinal microflora and/or its activities. The consequences of our modern lifestyle include an increase in inflammatory disorders such as allergy and autoimmunity, and this is driven by the effect that dysbiotic microbes have

on the epigenetic expression of immune system function.

One note of interest involving the role of stress on dysbiosis: when we are under stress, increasing levels of norepinephrine can spillover through simple diffusion into the gastrointestinal lumen where norepinephrine acts as a growth inducer to pathogenic microbes. So, when stressed we are feeding the growth of harmful microbes. Wellness involves more than nutrition and exercise. Stress reduction also plays a key role.

Most importantly, a healthy microbiome provides colonization resistance, or protection against colonization of the intestinal tract with potentially pathogenic bacteria afforded by the intestinal flora. Finally, 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.

As evidenced in the literature, the foods we choose impact our microbiome and therefore 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. Indeed, it can be said that we change the diet to change the microbes.

THE CONJUNCTIVAL MICROBIOTA

This microbial community of the ocular surface is more diverse than that of the skin but contains significantly fewer numbers 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), containing more gram-negative species. Further research is needed to determine if the increased risk of eye infections in contact lens wearers is related to contaminating the lenses with bacteria from the skin of the finger or if contact lenses exert selective pressures on the eye bacterial community in favor of skin bacteria.

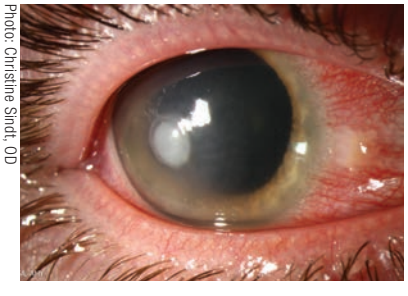


Photo: Christine Sindt, OD

FIG. 2. Patients with compromised ocular microbiota can be at higher risk for *Pseudomonas* ulcers, studies have shown.

Studies have not shown significant differences in the conjunctival microbiome between Sjögren's patients and controls; however, severe intestinal dysbiosis was identified in a recent study of 35 Sjögren's patients vs. age- and sex-matched controls.[10]

The intestinal microbiome of Sjögren's patients has been found to have less diversity than that of controls. A less diverse microbiome is considered a risk factor for inflammatory disease. As an aside, oral antibiotics largely contribute to reduced diversity of the intestinal microbiome and is one more reason to be scrupulous in their use.

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 conjunctival microflora due to the colonic microflora's ability to modulate the immune system and create inflammation and autoimmunity elsewhere in the body.

Interventions for Gut Microbial Flora

Exogenous bacteria can influence the dysbiotic gut to restore a healthy flora. These bacteria can be introduced in the form of probiotics or fecal microbiota transplantation, each with its own advantages and disadvantages. Microbes present in the environment can also alter the endogenous gut microbiome composition and confer disease susceptibility or protection, particularly when exposure occurs during infancy.[12]

Probiotics
Advantages: Oral application; restoration of good bacteria and gut barrier.
Disadvantages: Oral dose that reaches the gut varies; potential loss of adaptation of culture-derived probiotics in the gut.

Fecal Microbiota Transplantation
Advantages: Safe application; simple procedure.
Disadvantages: Variable impact; not very effective in IBD; quality of donor stool is important.

Environment
Advantages: Early-life exposure to microbes improves later-life immunity.
Disadvantages: Not qualitative/quantitative; mechanism of effect unknown.

IN SEARCH OF SYMBIOSIS

Treatment of intestinal dysbiosis through intake of foods and substances shown to support gut homeostasis includes prebiotics, probiotics, antibiotics, fecal microbiota transplantation, exercise and stress-relieving activities.

- ***Prebiotics*** typically consist of foods that support normal gut microbiome and 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 species generally promote intestinal barrier integ-

rity, prevent bacterial translocation in the gut and reduce inflammatory response.[12]

• ***Fecal microbiota transplantation***, also known as fecal bacteriotherapy or fecal infusion, an emerging method to treat dysbiosis, is described in a recent article as using "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."[12]

SYSTEMIC AND OCULAR DISEASES

Genetic pre-disposition has a role in disease; however, the range of environmental influences that impact human microbiota homeostasis include micronutrient intake, stress, medications, exercise, alcohol, smoking, glyphosate, *Candida* fungal overgrowth from excess sugar consumption and other toxic substances.[11]

Disease states implicated in dysbiosis include a wide range of disorders that include inflammatory bowel conditions, obesity, allergic disorders, Type I and II diabetes, autism, colorectal cancer, atherosclerosis, rheumatological disease, mood disorders (e.g., depression) and neurodegenerative conditions such as multiple sclerosis.[12]

Ophthalmic disorders directly impacted by microbiome dysbiosis include neuroretinal conditions such as age-related macular degeneration, diabetic retinopathy and glaucoma. Inflammatory eye conditions such as uveitis and Sjögren's disease have dysbiosis associations.

Advising patients to eat for a healthy microbiome is based on emerging science. Eating a diverse diet rich in whole foods, plants, fermented foods and healthy oils such as omega-3s from fish encourage a healthy microbiome. Avoiding oral antibiotics unless necessary is vital.

Optometrists Should Begin to Think "Inside Out"

- 95% of serotonin is made in your gut.
- 70% of your immune cells are in your gut.
- Your gut is a factory for making vitamins such as K2.
- Acne rosacea and periorbital skin diseases encountered in practice are modulated by gut bacteria.

THE EYE-BRAIN-GUT AXIS

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. ❍

1. Galland L. Gut microbiome and brain. J Med Food. 2014.
2. Hooks KB, O'Malley MA. Dysbiosis and its discontents. mBio. 2017;8:e01492-17.
3. Hippocrates. In: Lagasse P, Columbia University. The Columbia encyclopedia (7th ed.). New York, NY: Columbia University Press, 2017.
4. Hugenholtz, et al. Impact of Culture-Independent Studies on the Emerging Phylogenetic View of Bacterial Diversity. J Bacteriol. 1998 Sep; 180(18): 4765–4774.
5. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett C, Knight R, Gordon JI. The human microbiome project: exploring the microbial part of ourselves in a changing world. Nature. 2007;449(7164):804-810.
6. National Institute of Health: https://commonfund.nih.gov/hmp.
7. Bien J, Palagani V, Bozko P, et al. The intestinal microbiota dysbiosis and Clostridium difficile infection: is there a relationship with inflammatory bowel disease? Ther Adv Gastroenterol. 2013;6:53–68.
8. Kim D, Zeng MY, Núñez G. The interplay between host immune cells and gut microbiota in chronic inflammatory diseases. Exp Molecular Med. 2017;49:e339.
9. Srinivasan S. More Easily Cultivated Than Identified: Classical Isolation With Molecular Identification of Vaginal Bacteria. J Infect Dis. 2016 Aug 15;214(Suppl 1):S21-8.
10. Mandl T, Marsal J, Olsson P, Ohlsson B, Andreasson K. Severe intestinal dysbiosis is prevalent in primary Sjögren's syndrome and is associated with systemic disease activity. Arthritis Res Ther. 2017;19:237.
11. O'Connor EM. The role of gut microbiota in nutritional status. Curr Opin Clin Nutr Metab Care. 2013;16(5):509-16)
12. DeGruttola, Arianna K. et al. Current Understanding of Dysbiosis in Disease in Human and Animal Models. Inflammatory bowel diseases 22.5 (2016): 1137-1150.

Autoimmunity and the Gut

Like allergy and inflammation, autoimmunity represents immune system dysfunction in which the organism acts against its own healthy cells and tissues. Autoimmune diseases are the third leading cause of morbidity and mortality in the industrialized world, surpassed only by cancer and heart disease. It is estimated that 20% of Americans have an autoimmune disease.

Autoimmunity results from interactions between genes, infections, the gut microbiome and the environment. An imbalance between effector and regulatory T-cells (Treg) underlies the loss of immune tolerance to self-antigens in autoimmune disease.[1] About 70% to 80% of immune cells in the body are located in the gut-associated lymphoid tissue (GALT), and Tregs that are generated in the GALT travel to distant sites.[2] Recent studies have identified a key role for the gut microbiota in the development of intestinal Tregs.[3,4]

Orally administered probiotics have been shown to regulate immunomodulation.[4] The importance of diet and gastrointestinal dysbiosis can not be overstated. The 'good' bacteria of the gut rely on nutrients (e.g., vitamins A and D) and probiotics to induce tolerance; their absence predisposes the individuals toward metabolic, allergic and autoimmune inflammatory disorders.[5]

Since our microbiome is determined by our choice of foods, antibiotic exposure, prescription medicines, toxin exposure and stress, minding our microbiome is emerging as a necessary tool to promote health and wellness and shift our bodies away from a proinflammatory state.

1. Holder et al. Retinoic acid stabilizes antigen-specific regulatory T cell function in autoimmune hepatitis type 2. J Autoimmun. 2014 Feb 21.
2. Pabst O. Trafficking of regulatory T cells in the intestinal immune system. International Immunology. 2013 Mar 1.
3. Smith P, Garrett, W. The gut microbiota and mucosal T cells. Frontiers in Microbiology. 2011 May 26.
4. Kwon et al. Generation of regulatory dendritic cells and CD4+Foxp3+T cells by probiotics administration suppresses immune disorders. Proc Natl Acad Sci. 2010 Feb:2159-64.
5. Vasquez A. 2016 Human Microbiome and Dysbiosis in Clinical Disease. Peer-reviewed and distributed by the International College of Human Nutrition and Functional Medicine (www.ichnfm.org).

Windows into Wellness: Eight Biomarkers You Should Know

Expert advice from a pathologist can help you uncover the root cause of disease.

BY STUART RICHER, OD, PhD, KERRY GELB, OD, AND RUSSELL JAFFE, MD, PhD

The conventional view of health is absence of disease or infirmity. Yet the processes happening at a molecular level that determine our propensity for disease remain almost wholly invisible to us, making "absence of disease" a poor yardstick of health. As the saying goes, you don't know what you don't know.

But what if you could? Optometrists and most physicians are comfortable addressing symptoms or consequences. If you come out of your comfort zone, you can discover opportunities for physiological recovery and disease prevention years or even decades before symptomatic involvement would occur. Predictive biomarkers yield clues to processes that govern health (*Table 1*). The eight discussed below address the 92% of lifetime health risk and resilience that encompass epigenetics.

Table 1. Normal vs. Desirable Physiologic Predictive Goals

Predictive lab goals for optimal health are not the typical statistical ranges of normality, but science-based predictive characteristics for a healthy human body.

Biomarker	Typical 'Normal' Ranges	Best Outcome Predictive Goals
1. HbA1c (%)	4–6	<5
2. hsCRP (mg/L)	1–3	<0.5
3. Homocysteine (µmol/L)	4–17	<6
4. LRA	NA	Immune tolerance
5. First AM urine pH	4.6–8.0	6.5–7.5
6. 25-OH Vitamin D (ng/ml)	20–40	50–80
7. Omega 3 index (%)	ND	>8%
8. 8-OHdG (ng/mg creatinine)	4.6–19.2	<5

In fact, optometrists already routinely use three (HbA1c, hsCRP and vitamin D status) of these. This guide reviews them plus five others, all of which together comprehensively address the immune system. Several of these and other tests can be accomplished at home by patients themselves under your guidance.

Here, The Ocular Wellness and Nutrition Society presents the work of Russell Jaffe, MD, PhD, a board-certified clinical pathologist. He served at the Clinical Center (1975-79) after completing his pathology residency at the National Institutes of Health, where he was a US Public Health Service Officer from 1973-79.

As this is a complex topic, we provide the high-level overview here; readers interested in more detail can learn more at: www.ocularnutritionsociety.org and www.healthstudiescollegium.org.

1 HEMOGLOBIN A1c STATUS

Sugar and its derivatives attach to the hemoglobin (Hb) protein in red blood cells (RBCs) with a lifespan of three months. HbA1c levels are an effective way to observe blood sugar over that time frame. Normal HbA1c levels are considered 4% to 5.6%. If HbA1c increases by 1%, the risk of myocardial infarction triples.

Pre-diabetic patients present with an HbA1c level

between 5.7% and 6.4%. Values greater than 6.5% are considered diabetic. According to the Diabetes Control and Complication Study, lowering HbA1c levels can reduce instances of retinopathy by 76%, neuropathy by 60% and nephropathy by 50%. Monitoring HbA1c allows us to infer insulin resistance that accompanies the three major killers in the United States: cardiovascular disease, cancer and Alzheimer's.

The least risk/best outcome value for HbA1c is <5%.

Another marker of sugar stuck onto protein is fructosamine, whose half life is about a month. When red cell survival or marrow functions are uncertain, fructosamine measurement is recommended. Fructosamine <150µmol/L is the goal or best outcome value.

2 HIGH SENSITIVITY C-REACTIVE PROTEIN

Chronic inflammation is the body's major manifestation of a 'repair deficit' and a core conceptual component in understanding why humans get chronic degenerative diseases. High sensitivity C-reactive protein (hsCRP) is a non-specific liver marker induced in proportion to systemic inflammation. Normal levels range between 1mg/L and 3mg/L. Higher levels correlate with greater risk of heart attack; 2.4mg/L constitutes a doubling of cardiovascular-related events compared with levels below 1mg/L. Concentrations of 10mg/L or higher are typical of a non-cardiovascular etiology, such as infection or underlying malignancy.

Predictive biomarkers yield clues to processes that govern health.

Optometrists use this test along with the Westergren Sedimentation Rate and white blood cell count to rule out acute vision-threatening immune complex–induced arteritic (inflammatory) temporal arteritis. Studies show that elevated hsCRP predicts a 50% increased risk of developing dry and wet age-related macular degeneration (AMD). Type I diabetes patients presenting with elevated hsCRP have an 80% increased risk of clinical macular edema.

Pearls:

• Inflammation plays a major role in all modern chronic diseases.

• Be cognizant of 'inflamm-aging"—inflammatory cytokines increase fourfold with age due to cumulative deficits of essential nutrients and/or increasing toxin burden.

• The distinguishing characteristic of Japanese 'supercentenarians' (i.e., 110 years or older) is their lower hsCRP and not longer chromosome telomere length.

• In the battle against inflammation, turmeric, which contains curcumin, has emerged as a wonder drug. Curry is a health-promoting source of turmeric often used in Indian dishes. Turmeric supplements are often combined with biopterine (black pepper extract) to improve uptake.

3 HOMOCYSTEINE OXIDANT STATUS

An amino acid produced during protein metabolism, homocysteine (HCY) is a byproduct of the methylation process that's vital to thinking, repairing DNA, activating genes, fighting infections and removing environmental toxins. It is influenced by intake of vitamins B12 and folate. Optimal health is achieved with lower HCY; high levels could signal a breakdown in biochemical wellness. Concentrations greater than 9µmmol/L are often indicative of an atherogenic oxidation state in which platelets adhere to each other, increasing the chance for heart attack, stroke, pulmonary embolism, clot formation, carotid artery disease, miscarriage and potentially Alzheimer's disease.

In eye care, elevated HCY can contribute to AMD, cataracts and psuedoexfoliative glaucoma. High levels may manifest on fundus exams as retinal hemorrhages, exudates, cotton wool spots, optic atrophy and accelerated Scheie 3 arteriolarsclerotic-hypertensive retinopathy.

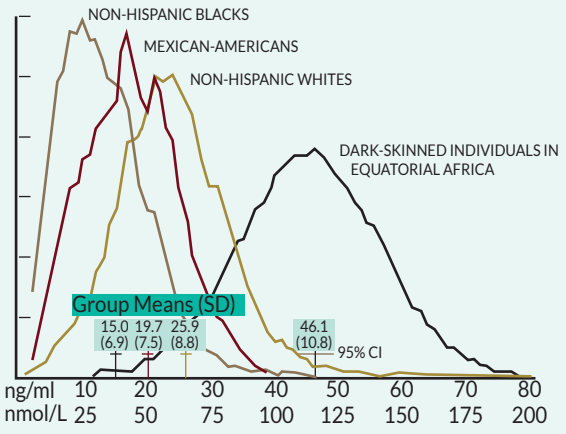
Providing nutritional protection for proper functioning of the methionine cycle may improve methylation and mitigate damage. To reduce HCY levels, it is essential to ensure proper digestion and metabolism and appropriate levels of B vitamins (in particular B12) and folate, magnesium and ascorbate by supplementation, in most cases. As such, always test for B12 and folate levels in patients complaining of peripheral tingling of toes, a metallic taste in the mouth, low back pain or low-tension glaucoma.

The physiologic form of B12 (hydroxocobalamine) is recommended rather than pharmacologic forms such as methyl-B12 or adenosyl-B12; uptake is better than a dot or lozenge dissolved under the tongue.

4 LYMPHOCYTE RESPONSE ASSAY

The goal of this health biomarker is to allow the human body to become stronger and more 'immune tolerant" as it removes individual sensitivities while providing nutrients that support the immune system.

Fig. 1. US Population Disparities in Vitamin D Status



Distribution of vitamin D in four populations—100% of each group lies below its line. Smoothed by averaging each set of three adjacent data points.

The lymphocyte response assay (LRA), introduced by Dr. Jaffe in 1984, is a biologic response assay that uncovers root causes of autoimmunity such as exposure to foods, additives, preservatives, toxins, medications, mold, dander, hair, feathers, herbs and other antigens to which individuals have become hypersensitive.

The LRA assay makes use of as many as >500 cell cultures directly related to autoimmune chronic inflammatory disease and degeneration states. Clinically, it helps distinguish immune tolerance from intolerance.

What does this mean for you? The LRA can prompt eye care practitioners and their patients to initiate strategies to identify toxins, correct nutritional deficiencies or strengthen digestion, to ultimately improve cellular repair and eye health. Tolerant immune systems repair efficiently and eliminate abnormal cells by apoptosis.

5 pH BALANCE AND MINERAL STATUS

Most Westerners have blood chemistry that is too acidic. This means anabolism (or "biosynthesis")—the constructive metabolism and synthesis of complex substances such as proteins and nucleic acids from simpler ones—is compromised. Catabolism is a destructive process involving the breakdown of complex molecules and formation of simple molecules. The balance between anabolism and catabolism is crucial, or fundamental cellular processes will end up in a kind of survival mode.

Measuring the first morning urine pH status (accomplished by patients at home with finely calibrated pH test strips) can reveal acidity of body chemistry and predict cellular mineral status, in particular magnesium levels. Most Americans are deficient in magnesium, zinc and potassium and replete in calcium, copper and sodium. A spot check of extracellular serum magnesium should be in the upper half of the laboratory range. Being in the lower half suggests chronic intracellular deficiency of this essential mineral.

6 25-OH VITAMIN D LIVER RESERVE STATUS

New research suggests that some Americans spend 24/7 living indoors and never see natural sunlight or breathe fresh air. The role of vitamin D includes immune modulation and prevention of diseases such as cancer and Alzheimer's. Lower vitamin D status is associated with all stages of AMD, and a larger area of post-bleed fibrosis of the retina.[1] The incidence of epithelial cancers of the breast, ovary and colon increase dramatically at northern sun-deprived latitudes. Ethnicity (skin pigmentation) plays a strong modulating role, as research suggests individuals with darker skin typically require higher doses *(Figure 1)*.

Best outcome range for vitamin D is 50ng/ml to 80ng/ml (*Table 2*). Since intestinal uptake in many adults is often compromised, we suggest drops (500IU/drop) under the tongue so this neurohormone goes to the brain and then the rest of the body at levels sufficient to bring the individual into the best outcome goal range.

7 RBC CELL MEMBRANE OMEGA-3/OMEGA-6 BALANCE

This test measures the percent of red blood cell membrane omega-3 fatty acids (EPA and DHA combined) and may be a better indicator of chronic vascular disease risk than cholesterol. A high omega-6/low omega-3 ratio is characterized by impaired repair, increased inflammation, immune imbalance and immune Th1- and Th2- mediated diseases.[2,3]

The average American maintains a value of about 5%, yet erythrocyte EPA and DHA levels are almost twice those of Western populations in Japan, where fish consumption is high.[4] Individuals should consume oily fish three times per week along with omega-3 supplementation. The triglyceride form of fish oil is 15% better at raising the index compared with the traditional ethyl ester form. The best outcome goal value is >8%.

Table 2. The 25-OH Vitamin D Liver Reserve Status Test

Values expressed as ng/ml.

<20	deficient, yet common
20-32	insufficient
>32	sufficient
40-60 or 50-80	best outcome range
120-150	safety unknown

Pearl:

• A high omega-6/low omega-3 ratio is characterized by increased inflammation, immune imbalance and greater rates of innate Th1 immunity as well as Th2 delayed immunity diseases.

8 OXIDATIVE STRESS ASSESSMENT OF URINE OR SKIN

Measuring oxidative stress using urine or skin (e.g., Pharmanex BioPhotonic scanning) noninvasively determines the amount of cellular oxidative stress from free radicals (i.e., hydroxyl, superoxide, N radicals, H_20_2). Biomarkers of oxidative stress are relevant in evaluating disease status.[5] Research has revealed widespread involvement of oxidative stress in a number of disease processes, including cancer, cardiovascular disease, atherosclerosis, diabetes, arthritis, neurodegenerative disorders and pulmonary, renal and hepatic diseases.[5] These states have increased incidence with age, and oxidative stress may be a factor in aging and age-associated diseases.[5] As such, oxidative stress markers are important tools to assess disease states and progression and the health-enhancing effects of antioxidants.

Oxidized nucleotides are excreted into the urine, and their measurement has been shown to be predictive of the development of several diseases. For example, high levels of DNA oxidation, measured as urinary excretion of 8-OHdG, is predictive for the risk of breast and lung cancer, atherosclerosis and diabetes.[5]

Advanced glycation end products (AGEs) increase with aging, and their formation is related to carbohydrate intake. High AGEs in turn are linked to diabetes and obesity, as well as other diseases including atherosclerosis, Alzheimer's disease and renal insufficiency.[5] Some promising results have come from studies on human lens and skin autofluorescence in diabetic patients, although the lens and serum fluorescence AGE method has limitations.[5] ❍

1. Layana AG, Minnella AM, Garhöfer G, et al. Vitamin D and age-related macular degeneration. Nutrients. 2017;9(10):1120.
2. Simopoulos AP. The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. Exp Biol Med (Maywood). 2008;233(6):674-88.
3. Ahmed N, Barrow CJ, Suphioglu C, et al. Exploring the effects of omega-3 and omega-6 fatty acids on allergy using a HEK-Blue cell line. Int J Mol Sci. 2016;17(2):220.
4. National Eye Institutes. Fact Sheet for Health Professionals: Omega-3 Fatty Acids. https://ods.od.nih.gov/factsheets/Omega3FattyAcids-HealthProfessional. Accessed August 23, 2018.
5. Marrocco I, Altieri F, Peluso I, et al. Measurement and clinical significance of biomarkers of oxidative stress in humans. Oxid Med Cell Longev. 2017;6501046.

Additional Cardiovascular 'Vertical Serum' Lab Tests to Consider

Nearly 200 systemic diseases can manifest in the eyes. Given that optometrists are often the first health care providers to diagnose and manage acute and chronic disease, ODs have become the new primary care physician, according to OWNS Board member Lisa Renzi Hammond, PhD. As such, it's important to be aware that typical routine blood work is often not sensitive enough to pick up very early vascular disease. Advanced biomarker testing beyond common cholesterol, LDL, HDL and triglycerides are often necessary to diagnose 'accelerated aging' beyond that caused by smoking, genetic and other environmentally modulated high-risk arteriolarsclerotic retinopathy. Here are important in-house and conventional laboratory tests to consider:

• ***Blood insulin.*** This is one of the earliest markers for prediabetes, diabetes, kidney and cardiovascular disease. Optometrists who find microaneurysms during retinal exams can often confirm hyperinsulinemia with a fasting and two-hour insulin assay. Ideally, measure at 30-minute intervals post-fast, up to five hours after the patient ingests 100g of glucose. Insulin resistance denotes greater than 40IU/mL on a two-hour insulin assay. (Drs. Gelb and Richer have published research showing insulin measures correlate with subclinical retinal microaneurysms, in otherwise 'normal' non-diabetic individuals, using multispectral retinal imaging.)

• ***Lipoprotein A.*** This is a small, dense sub-fraction of LDL cholesterol considered to be inflammatory and pro-atherogenic. Retinal vein occlusions can be caused by elevated lipoprotein A. Desirable concentrations vary by race, but very high-risk cardiovascular disease patients often have levels greater than 50mg/dL. Check with your lab. Optometrists can determine this important factor for retinal hemorrhage and branch vein occlusion, and prescribe vitamin C and CoQ10 to keep levels in check.

• ***Fibrinogen.*** A liver protein classified as an acute phase reactant, fibrinogen (FBG) acts non-specifically in response to conditions such as infection, inflammation or other events that cause stress. Decreased FBG leads to inadequate coagulation and increased bleeding, while elevated levels are a biomarker for cardiovascular disease, overclotting and increased risk for a heart attack. FBG is also elevated in smokers and patients with AMD and serves as an additional biomarker for retinal hemorrhages.

• ***Ferritin.*** Measuring this acute phase reactant offers an indirect way to detect low or high iron storage. Low ferritin levels can result in iron deficiency, anemia or a decrease in red blood cells. Elevated ferritin occurs in genetically susceptible patients with hemochromatosis, as well as red meat eaters. The result is heightened risk of heart disease, diabetes, neurodegenerative disease, cancer, gouty arthritis and other health issues. Optimal levels are between 40ng/dL and 60ng/dL. Normal levels are between 20ng/dL and 80ng/dL (less than 80ng/mL for women and less than 90ng/mL for men) and can be determined with a $10 lab test. Providing a liter of donated blood can lower serum ferritin by 30 points.

• ***Vitamin C redox status.*** Vitamin C sets the redox potential of all human cells. Yet health authorities tell us 60 to 200 milligrams/day is sufficient to avert scurvy (i.e., bleeding gums, fatigue, anemia, painful joints, shortness of breath, lassitude) even if you smoke cigarettes, take diuretic water pills, steroids or aspirin, all of which deplete vitamin C. The amount of vitamin C required by an individual varies widely but can be determined with an at-home bowel tolerance test. Instructions available at www.perque.com.

The Good Life: Five Ways to Integrate Wellness

Exercise, health consciousness and a positive mental attitude complement diet and supplementation.

BY STUART RICHER, OD, PhD

Physical activity is fundamental for health and wellness now more than ever, given our sedentary and screen-dominant society. We should all be cognizant of our body's need for movement. This is a crucial aspect of the "wellness" component of OWNS: combining physical activity with a well-balanced nutrition plan. Both are fundamental. One cannot simply exercise oneself out of a bad diet or, conversely, be scrupulous about a good diet while never engaging in physical activity.

To round out the education provided in this supplement, here are five simple principles to encourage your patients—and yourselves.

1 FIND SMALL, DAILY VICTORIES

Look for little ways to increase the number of calories you burn every day: use the stairs instead of the elevator, walk to and from your car instead of using the valet, go for a walk with your significant other, especially after a full meal. Sunlight exposure during a walk also improves mood and increases vitamin D production. Remember to bring along water with minerals. Good hydration throughout the day supports countless bodily functions.

2 FOCUS ON FITNESS

Body composition, and not necessarily body mass index (which relies on height and weight), has a direct

The author, practicing what he preaches, shows off good form on a Gyrotonic machine.

General Principles for a Thoughtful 45-minute Workout

Start your workout routine with a low-impact 10-minute flexibility and stretch regimen that works both the upper and lower body.

Next comes a 20-minute strength training routine focusing on your major muscle groups and core to build strength and mass. This is typically done with free weights and/or rubber stretch bands. The bands can be thrown in a suitcase for travel, and can be used in the office while waiting for your computer to initialize in the morning or even between eye examinations. Your patients will be impressed—and you'll be practicing what you preach. You are going to want to work the following muscle groups: chest, biceps, legs, back, obliques, shoulders and triceps.

For those serious about improving their balance while weight lifting, the 'free weights' can be combined with a balance trainer platform (e.g., Bosu) or Swiss Ball with supervision. The exercise physiologist can also direct you to the best gym equipment to complement the free weight / balance exercises.

Finally, a 12-minute high-intensity interval training (HIIT) session is the most efficient way to improve cardiovascular fitness, if cleared by your physician. HIIT exercise relies predominately on the ATP-PC (high power, short duration) and glycogen stored in the muscle fibers. HITT could involve a 3/1 routine with three repetitions, such as three minutes of high-intensity all-out cycling followed by one minute of a low intensity recovery, all repeated three times.

Now that you are finished, it's best to have those carbohydrates you've deprived yourself of all week—to build up your depleted glycogen stores.

impact on your health, athletic performance and even life expectancy. Age-adjusted body fat percentage is the best way to determine your level of fitness: it must be low enough to achieve peak performance yet high enough to cushion and protect organs and reduce the risk of injury. Weight loss alone without exercise can actually decrease your lean mass and increase your body fat percentage beyond that associated with aging.

3 KEEP IT FUN

Above all, physical activity must be fun or few will partake in it. America has more health clubs and home exercise equipment than any other country yet remains the most obese population in the world.

The three major types of exercise are *flexibility*, *strength training* and *cardiovascular*—and should be performed in that order. For patients unenthused about going to the gym, this trilogy of activities can be found in the minimal-impact activities of swimming and yoga.

A workout regimen also has to fit your life, not disrupt it. An exercise physiologist can individualize a realistic program. If someone only has a half hour or full hour per week, they should find a trainer who will customize a program around that schedule instead of imposing their own. This is supposed to be enjoyable.

Patients need to have a plan when buying and using gym equipment, either at home or at the health club. Gym equipment should be selected that adds elements of balance and coordination, as steadiness and stability become increasingly impaired with age. Simple items such as stretch bands, Swiss Balls and balance trainer platforms are inexpensive tools.

4 CLEANSE THE SYSTEM

Detoxification is typically not addressed in the examination room but is important because it will ultimately impact your patients' eye and brain health in profound ways.

The liver plays major role in the inactivation of multiple substances, including hormones, steroids, toxins and drugs. It contains the body's chief drug metabolizing enzyme: cytochrome P450. Variability in P450 performance between individuals is why the same dosage of a drug can have patient-specific differences in effect, potentially leading to either a toxic dose (in under-metabolizers) or an insufficient dose (in hyper-metabolizers).

If not for the proper function of the liver, the various substances secreted by our body (such as insulin) could remain in a constantly active form, throwing our body out of homeostasis and leading to various diseases. When the body accumulates an excess of toxic substances that the liver cannot convert into inactive substances, hepatocyte damage sets in (i.e., alcoholic cirrhosis and non-alcoholic fatty liver disease).

Natural detoxifiers include sulfur-rich foods such as garlic, ginger, onions, Brussels sprouts and eggs. Encourage their consumption among your patients—along with a goal of moderation in intake of alcohol.

5 GET SOME REST

We spend a third of our lives sleeping—or at least we should. American society values ambition and drive, which diminishes the importance of rest, stress relief, and physical and mental downtime. Poor or insufficient sleep negatively impacts mood, hormone function, mental sharpness and kindness toward others. Patients should refrain from caffeine use at least six hours prior to sleep, and restrict digital device use in the hours prior to bedtime as the light of illuminated screens disrupts melatonin levels. ❍