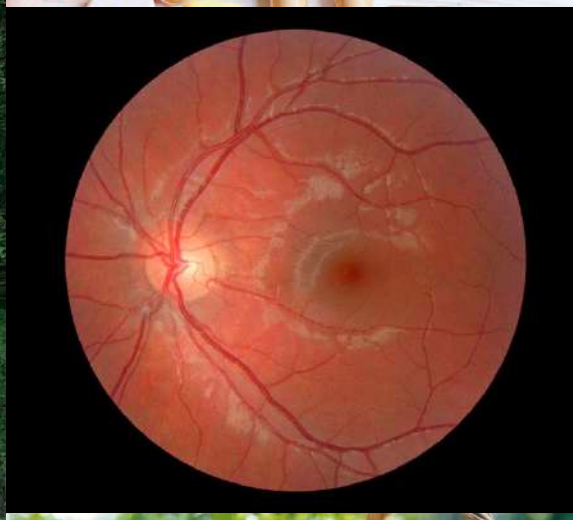

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OCULAR HEALTH AND WELLNESS:

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[1]Data on file for #1 Doctor Recommended Brand, Bausch + Lomb. [2]Age-Related Eye Disease Study 2 Research Group. AREDS2 randomized clinical trial. JAMA. 2013;309(19):2005-15. [3]https://nei.nih.gov/areds

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OCULAR HEALTH AND WELLNESS:

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‘Eyes and Feet’ and the Power of Helping People See

BY JULIE POTEET, OD, MS, CNS, FOWNS

I spent one of my optometry school summers with homeless veterans in Boston. I began to appreciate just how important our sense of sight truly is when I volunteered with my beloved professor, Dr. Dan Kurtz, who ran the eye clinic at the New England Center and Home for Veterans downtown. I remember Dr. Kurtz’s words as if it were yesterday, “Eyes and feet, that’s what these homeless veterans are most worried about.” That summer, I truly learned the power of helping people see.

Survey after survey has shown us that of all our senses, people value their sense of sight the most. As eye doctors, helping people see is a profound privilege that involves more than glasses or contact lenses. With great privilege comes great responsibility, an often overused but true aphorism. Preserving ocular health is the responsibility of every eye care practitioner.

Nutritional Health on a National Level

We as a profession cannot ignore the power of nutrition or lifestyle changes to mitigate the risk or course of ocular disease. Researchers at the Food is Medicine Institute at the **Friedman School of Nutrition Science and Policy** at Tufts University recently released a report that showed that incorporating targeted food and nutrition strategies into health care on a national level will improve health and quality of life, reduce work for hospitals, and cut health care costs.

The **True Cost of Food: Food is Medicine Case Study** revealed that implementing food is medicine strategies would save U.S. lives and billions of dollars each year.

What You Will Learn from This eResource

In this valuable eResource brought to you by the **Ocular Wellness & Nutrition Society** (OWNS) and ***Review of Presbyopia and the Aging Eye,*** you will learn how nutrients and lifestyle factors can be used to mitigate the course of ocular disease and promote wellness. Food carries information, molecules, instructions, and code that program your biology with every bite for better or worse. Industrial food drives inflammation, triggers oxidative stress, promotes imbalances in hormone and brain chemistry, overloads your detoxification system, depletes your energy, damages your microbiome, and changes your gene expression to turn on disease-causing genes. Real, whole nutrient and phytonutrient-rich food does the opposite. It turns off inflammation, increases antioxidant systems, balances hormones and brain chemistry, boosts detoxification, increases energy, optimizes your microbiome, and turns on disease-preventing health-promoting genes.

Encompassing wellness practices involves more than food. Sometimes it’s not what you’re eating, it’s what’s eating you. Chronic stress causes gut bacteria to be more toxic, but stress can be relieved through meditation

Dr. Julie Poteet with Admiral James Stavridis at the 2022 U.S. Global Leadership Coalition, where the man who sent warships into battle cited his most profound moment, observing an optometrist helping a child with high myopia in a remote village see.

OWNS board members and honored students at the American Academy of Optometry 2023: (from left) **Dr. Kaleb Abbott, UAB student Steven Chen, Dr. Neda Gioia, Dr. Julie Poteet, and SUNY student Rebecca Treen.**

or exercise. Also, sleep hygiene and daily movement are pillars of wellness and vitality.

Ocular Wellness & Nutrition Society

OWNS is the professional society for doctors with an interest in nutrition and wellness. Through our board of directors' hard work, we now have alliances with the major professional nutrition societies in North America. Our goal is to be a bridge connecting research scientists to clinicians who implement the latest evidence-based recommendations on nutrition and wellness practices to their patients. Fueled in part by post traumatic growth from the global pandemic of COVID leading to a renaissance of health, we have entered into **The Age of Scientific Wellness.** We can now measure so many different parameters of health that it is confusing to patients and practitioners alike. In a society filled with much erroneous nutrition and wellness information, OWNS serves as a source for evidence-based recommendations.

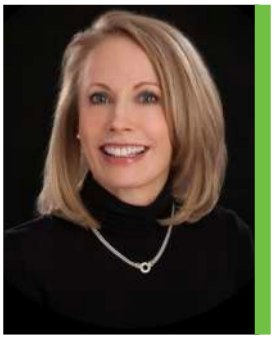
The Power of Gratitude

At the American Academy of Optometry's 2023 meeting in New Orleans, the plenary session centered on mental health. In her presentation, Bernadette Melnyk, PhD, Chief Wellness Officer and Dean of Nursing at The Ohio State University, touched on the power of gratitude in medicine. She urges her students to think of three things they are grateful for every day as this has been shown in studies to promote wellness. Eye care practitioners have much to be grateful for.

In closing, I would like to share a personal story. In 2022, I attended the U.S. Global Leadership Coalition conference in Washington, D.C. The keynote speaker was Admiral James Stavridis, a retired four-star officer who led the NATO Alliance in global operations from 2009 to 2013 as Supreme Allied Commander. Admiral Stavridis ended his address by sharing a story. He said that he has sent warships into battle, but the most profound moments of his career were sending medical ships to serve. He ended his speech with his most profound moment – observing an optometrist helping a child with high myopia in a remote village see.

May we as a profession never take for granted the privilege we have in caring for sight. ■

Julie Poteet, OD, MS, CNS, FOWNS



Dr. Julie Poteet, OD, MS, CNS, FOWNS, graduated from The New England College of Optometry and then completed a residency in primary care and ocular disease at the VA Medical System in Boston. At the VA, Dr. Poteet became interested in why some veterans seemed to age so differently from their peers and began questioning what lifestyle factors have the greatest impact on health and vitality. She then went on to complete a Master of Science in Human Nutrition and Functional Medicine. After earning her Master's Degree, she then completed the requirements to become a Certified Nutrition Specialist in 2015, becoming one of the first ODs to attain CNS certification. Dr. Poteet served as Vice President of the Ocular Wellness & Nutrition Society (OWNS) for six years under her mentor Dr. Stuart Richer, and she served as President of OWNS for three years. She has lectured extensively on the microbiome and immune system dysfunction. She works in Atlanta, where her office is a Macular Degeneration Center of Excellence. She is a member of the American Nutrition Association, formerly the American College of Nutrition. Dr. Poteet is passionate about carrying on the legacy of her mentor, Dr. Stuart Richer, whose mantra "repair the roof before it starts raining" is an excellent metaphor for using lifestyle and nutrition to mitigate the course of disease.

Nutrition and Eye Care: A Historical and Contemporary Review of the Last Quarter Century

BY DENNIS RUSKIN OD, FAAO

The interplay between nutrition and health has fascinated scholars for over two and a half millennia. In this account, in the Old Testament, Daniel and his colleagues opted for vegetables and water over the king's luxurious fare, noticing improved health as a result.[1] Fast forward to 1747, and we encounter James Lind's pioneering experiment aboard the HMS Salisbury — often credited as the first controlled clinical trial — which discovered the curative properties of citrus fruits against scurvy.[2] These initial studies set the foundation for the continually advancing field of nutritional science, shaped by the changing dietary practices of societies throughout history. As Virginia Woolf astutely remarked, one cannot think well, love well, sleep well, if one has not dined well.[3] This insight captures the profound link between our dietary choices and overall well-being, extending even to our visual abilities.

In a modern context, non-communicable or lifestyle diseases, encompassing conditions such as diabetes, heart disease, and certain cancers are claiming more lives than their communicable counterparts. Research suggests that thoughtful interventions could prevent or lessen the severity of more than 75% of these conditions.[4] Here, nutrition emerges as a double-edged sword: while deleterious choices (e.g., nitrates in processed meats) can jeopardize health, beneficial selections, such as a Mediterranean-style diet rich in fresh produce, can bolster cardiovascular and ocular health. This dichotomy revives Hippocrates' timeless counsel, "Let food be thy medicine and medicine be thy food."

Historically, the U.S. nutrition landscape has witnessed remarkable shifts, commencing with extensive nutrition studies. These seminal works ranged from observational research on dietary habits to intricate clinical trials and pioneering genetic explorations. Gradually, the investigative lens expanded from isolated nutrients to encompass overarching dietary patterns. This broader perspective revealed the superior health advantages of Mediterranean diets over low-fat alternatives. Moreover, traditional views that focused narrowly on individual nutrients sometimes overlooked the complex interplay between diet and non-communicable diseases. The emphasis has since shifted toward understanding the benefits of holistic dietary patterns, which favor whole and minimally processed foods. Concurrent with these scientific revelations, diverse dietary trends gained traction. As the nutrition science horizon broadened, encompassing personalized nutrition, the symbiotic relationship between prebiotics and probiotics,[5] the nuanced role of specific fatty acids, and the sociocultural dynamics shaped our relationship with food.

Studies have highlighted a connection between nutrition, the gut microbiome, and its direct influence on the Retina-Gut-Brain axis.

In summary, the complex relationship between nutrition and eye health has garnered significant attention over the last 25 years. Yet, the diverse effects of nutrition on ocular health remain a topic of continuous discussion. See Table 1, which is a collection of landmark clinical studies spanning over the last quarter century that have impacted ocular health and visual performance. From these studies, we learn the intricate relationship between nutrition and ocular health, and several key lessons emerge that are pertinent for primary care providers:

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NUTRIENT EFFICACY:

Not all nutrients are created equal when it comes to ocular health. Specific nutrients such as lutein, meso-zeaxanthin, zeaxanthin, omega-3 fatty acids, and certain vitamins (e.g., vitamin C, E) have demonstrated marked benefits for conditions such as age-related macular degeneration.[6]

SUPPLEMENTATION STRATEGY:

The studies highlight the potential benefits of supplementation, especially for those with or at risk for ocular diseases. For instance, the AREDS and AREDS2 trials showed that a combination of specific vitamins and minerals could reduce the risk of AMD progression.

HOLISTIC APPROACH:

It's not just about isolated nutrients but their combination and overall dietary patterns. The interaction of multiple nutrients and their combined effect on eye health emphasizes the need for a balanced diet.[7]

PREVENTIVE POTENTIAL:

Many of the studies underscore the preventive potential of nutrition in ocular health, suggesting that timely dietary interventions can either delay the onset or reduce the severity of certain eye conditions.[8]

GENETIC CONSIDERATIONS:

Individual genetic makeup may influence the response to nutritional interventions. This was evident in the AREDS2 formulation where individual response to zinc may be influenced by genetics.[9]

CONTROVERSIES AND EVOLVING KNOWLEDGE:

As with all areas of medicine, our understanding evolves.

Table 1. - 19 Landmark Clinical Nutrition Studies Impacting Ocular Health and Visual Performance over the last quarter century

PUBLICATION DATE	CLINICAL STUDY
1996	**Distribution of Lutein and Zeaxanthin Stereoisomers in the Human Retina** **Conclusion:** It is proposed that lutein and zeaxanthin are transported into an individual's retina in the same proportions found in their blood serum. Some of the lutein is then converted into meso-zeaxanthin, primarily in the macula, by a mechanism that is less developed in infants than adults. Reference: Bone RA, Landrum JT, Friedes LM, Gomez CM, et al. Distribution of lutein and zeaxanthin stereoisomers in the human retina. *Exp Eye Res.* 1997 Feb;64(2):211-8.
1999	**Beaver Dam Eye Study** **Conclusion:** Higher dietary intakes of lutein and zeaxanthin were associated with a reduced risk of developing new cataract. Reference: Lyle, Barbara J., et al. Antioxidant intake and risk of incident age-related nuclear cataracts in the Beaver Dam Eye Study. *The American Journal of Epidemiology* 149.9 (1999): 801-809.
2001	**Age-Related Eye Disease Study (AREDS)** **Conclusion:** A combination of vitamin C, vitamin E, beta-carotene, and zinc can reduce the risk of advanced age-related macular degeneration (AMD) by about 25%. Reference: 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. *Archives of Ophthalmology* 119.10 (2001): 1439-1452.
2002	**Blue Mountains Eye Study** **Conclusion:** Found a strong association between dietary antioxidants (especially vitamin C) and a reduced incidence of cataract development. Reference: Mitchell, Paul, et al. Dietary antioxidant intake and incidence of early age-related maculopathy: the Blue Mountains Eye Study. *Ophthalmology* 109.12 (2002): 2272-2278.
2002	**Resonance Raman Measurement of Macular Carotenoids in Normal Subjects and in Age-related Macular Degeneration** **Conclusion:** Uses a novel technique called Resonance Raman spectroscopy to measure the macular pigments lutein and zeaxanthin in the eyes of subjects, establishing a method to non-invasively determine levels. Reference: Bernstein, P. S., Zhao, D. Y., Wintch, et al. Resonance Raman measurement of macular carotenoids in normal subjects and in age-related macular degeneration patients. *Ophthalmology,* 109(10), 1780-1787.
2002	**The Rotterdam Study** **Conclusion:** High dietary intake of beta-carotene, vitamins C and E, and zinc was associated with a substantially reduced risk of age-related macular degeneration in elderly individuals. Reference: Ho, L., et al. Reduced risk of age-related macular degeneration with high intake of antioxidants: the Rotterdam Study. *Journal of the American Geriatrics Society* 50.8 (2002): 1433-1434.
2004	**Lutein Antioxidant Supplementation Trial (LAST)** **Conclusion:** Lutein supplementation improved visual function in patients with atrophic age-related macular degeneration. Reference: Richer, Stuart, et al. Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial). *Optometry* 75.4 (2004): 216-230.
2006	**The POLA Study** **Conclusion:** Higher plasma concentrations of vitamin C reduced the risk of cataract formation. Reference: Delcourt, Cécile, et al. Plasma lutein and zeaxanthin and other carotenoids as modifiable risk factors for age-related maculopathy and cataract: the POLA Study. *Investigative Ophthalmology & Visual Science* 47.6 (2006): 2329-2335.
2007	**European Eye Study (EUREYE)** **Conclusion:** Dietary zeaxanthin and lutein intake was inversely associated with incident AMD. Reference: Augood, Cristina, et al. Oily fish consumption, dietary docosahexaenoic acid and eicosapentaenoic acid intakes, and associations with neovascular age-related macular degeneration. *The American Journal of Clinical Nutrition* 86.2 (2007): 328-334.

Table 1 - 19 Landmark Clinical Nutrition Studies Impacting Ocular Health and Visual Performance over the last quarter century

PUBLICATION DATE	CLINICAL STUDY
2007	**Singapore Malay Eye Study** **Conclusion:** Higher fish consumption, rich in omega-3, is linked to lower visual impairment prevalence in older adults. Reference: Chong EW, Kreis AJ, Wong TY, Simpson JA, Guymer RH. Dietary omega-3 fatty acid and fish intake in the primary prevention of age-related macular degeneration: a systematic review and meta-analysis. Arch Ophthalmol. 2008 Jun;126(6):826-33.
2007	**Macular Pigment Response to a Supplement Containing Meso-zeaxanthin, Lutein, and Zeaxanthin** **Conclusion:** For the first time we found that meso-zeaxanthin is absorbed into the serum following ingestion, indicating that a supplement containing predominantly meso-zeaxanthin is generally effective at raising macular pigment density. Reference: Bone RA, Landrum JT, Cao Y, Howard AN, Alvarez-Calderon F. Macular pigment response to a supplement containing mesozeaxanthin, lutein and zeaxanthin. Nutr Metab (Lond). 2007 May 11;4:12.
2008	**The Carotenoids in Age-Related Eye Disease Study (CAREDS)** **Conclusion:** Higher dietary intake of lutein and zeaxanthin was associated with a lower risk of developing advanced age-related macular degeneration. Reference: Moeller, Suzen M., et al. Associations between age-related nuclear cataract and lutein and zeaxanthin in the diet and serum in the Carotenoids in the Age-Related Eye Disease Study, an ancillary study of the Women's Health Initiative. *Archives of Ophthalmology* 126.3 (2008): 354-364.
2009	**Olive Oil and Retinal Diseases Study** **Conclusion:** Increased olive oil consumption is associated with a reduced risk of serious retinal diseases. Reference: Rumawas, Maria E., et al. Mediterranean-style dietary pattern, reduced risk of metabolic syndrome traits, and incidence in the Framingham Offspring Cohort. *The American Journal of Clinical Nutrition* 90.6 (2009): 1608-1614.
2009	**B-Vitamin Treatment Trial** **Conclusion:** Supplementation with folic acid, B6, and B12 reduced the risk of age-related macular degeneration. Reference: Christen, William G., et al. Folic acid, pyridoxine, and cyanocobalamin combination treatment and age-related macular degeneration in women: the Women's Antioxidant and Folic Acid Cardiovascular Study. *Archives of internal medicine* 169.4 (2009): 335-341.
2009	**Los Angeles Latino Eye Study** **Conclusion:** Higher omega-3 fatty acid consumption decreased the risk of diabetic retinopathy in type 2 diabetics. Reference: Chiu, Chung-Jung, et al. Dietary compound score and risk of age-related macular degeneration in the age-related eye disease study. *Ophthalmology* 116.5 (2009): 939-946.
2013	**Age-Related Eye Disease Study 2 (AREDS2)** **Conclusion:** Adding lutein and zeaxanthin, omega-3 fatty acids, or both to the original AREDS formulation did not further reduce risk of progression to advanced AMD. Reference: 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. *JAMA* 309.19 (2013): 2005-2015.
2015	**The Diabetes Visual Function Supplement Study (DiVFuSS)** **Conclusion:** There is strong evidence of improvements in visual function, hsCRP and peripheral neuropathy in patients with diabetes, both with and without retinopathy, and without affecting glycaemic control. Reference: A Paul Chous , Stuart P Richer , Jeffry D Gerson et al. *Br J Ophthalmol. 2016 Feb;100(2):227-34*
2017	**CREST (Central Retinal Supplementation Trials)** **Conclusion:** CREST is the first study to investigate the impact of supplementation with all three macular carotenoids. Supplementation of all these carotenoids resulted in an improvement in visual function among individuals with early-stage-related macular degeneration. Reference: Kwadwo Owusu Akuffo 1, Stephen Beatty, Jim Stack, et al. *Ophthalmic Epidemiol.* 2014 Apr;21(2):111-23
2023	**Alterations Of The Intestinal Microbiota In Age-Related Macular Degeneration** **Conclusion:** AMD patients had different gut microbiota compared with healthy controls, and that AMD pathophysiology might be linked to changes in gut-related metabolic pathways. Reference: Zhang Y, Wang T, Wan Z, Bai J, Xue Y, Dai R, Wang M, Peng Q. Alterations of the intestinal microbiota in age-related macular degeneration. Front. Microbiol., 05 April 2023 Sec. Systems Microbiology Volume 14 - 2023

For example, while omega-3 supplementation was once thought to significantly reduce cardiovascular disease risks, which could indirectly benefit ocular health, later studies revised this view.[10] Primary care providers need to stay updated with the latest research to provide the best advice to their patients.

WIDER HEALTH IMPLICATIONS:

Many of the nutrients beneficial for the eyes, such as omega-3s or polyphenols, also have systemic benefits, supporting cardiovascular health, cognitive function, and more. This interplay between ocular and systemic health underscores the importance of nutrition in comprehensive patient care.[11]

The Significance of AREDS

Before the groundbreaking AREDS clinical trials, the domain of ocular health largely operated in a vacuum with limited scientific research underscoring the role of vitamins and nutrients that mitigate visual risks. The inception of AREDS and its successor AREDS2 marked a pivotal turn in our understanding. These trials demonstrated that specific nutritional recommendations could decelerate the progression of AMD. This revelation meant that for the very first time, eye care professionals could tangibly bridge the chasm between nutrition and visual health, recommending a regimen of vitamins to curtail the risk of visual loss. The results from the study suggested that a specific formulation of antioxidants and zinc could reduce the risk of advanced AMD in some individuals.

The New Frontier: Nutrition and the Retina-Gut-Brain Axis

Beyond the direct impact of nutrition on eye health, the human microbiome, primarily located in the gut, emerges as a key player. The gut microbiome plays a pivotal role in our health, influencing not only our digestive system but also interacting with the retina and the brain. Recent studies have highlighted a connection between nutrition, the gut microbiome, and its direct influence on the Retina-Gut-Brain axis. This axis underscores the dynamic interplay between the retina, gut microbiome, and the brain, each affecting the others' health and functionality. While the gut-brain axis is a recognized concept, the potential interaction between the retina, an extension of the brain, and the gut is an emerging focus. The Retina-Gut-Brain axis[12] suggests a complex interconnection between gut health, retinal health, and cognitive function. A balanced gut microbiome might not only enhance ocular health but also influence cognitive function and potentially decelerate specific eye disease progressions.[13] Additionally, retinal health can hint at overall brain health, and visual inputs caused by changes to the circadian rhythm can affect gut functionality. Recognizing this axis might pave the way for new treatments targeting both ocular and neurological conditions. The profound connection between nutrition and eye health, especially within the context of the retina-gut-brain axis, is gaining clarity.

Over the last quarter century, the evolving landscape of nutrition has revealed significant connections between dietary habits and ocular health. For primary care providers, this historical context emphasizes the need to integrate the latest nutritional insights into patient care. Understanding these dietary milestones can empower eye care providers to guide patients more effectively, promoting not just ocular well-being but overall health. As we move forward, it remains essential to stay abreast of emerging research, ensuring that our recommendations reflect the best of both past wisdom and contemporary science. ■

Dr. Dennis Ruskin, OD, FAAO, graduated with an OD degree from the University of Waterloo in 1976. In 1989, he received a fellowship with the American Academy of Optometry. Dr. Ruskin has been an appointed advisory member to various committees within the Canadian provincial government, College of Optometrists of Ontario, Ontario Association of Optometrists, and pharmaceutical corporations. He is a past president of the College of Optometrists of Ontario (the regulatory body governing optometry in the province of Ontario), and he served as chair of the clinical practice committee of the college. He has also had a clinical affiliation with the Vision Institute of Canada and has served as examiner for the Canadian Examiners of Optometry. He lectures to eye care professionals in North America and has served as a clinical investigator with the Center for Ocular Research and Education (CORE) University of Waterloo. Dr. Ruskin has an interest in nutrition and its impact on ocular and systemic disease. He is a founding board member of the Ocular Wellness and Nutrition Society and founding past chair of the Ocular Nutrition Special Interest Group of the American Academy of Optometry.

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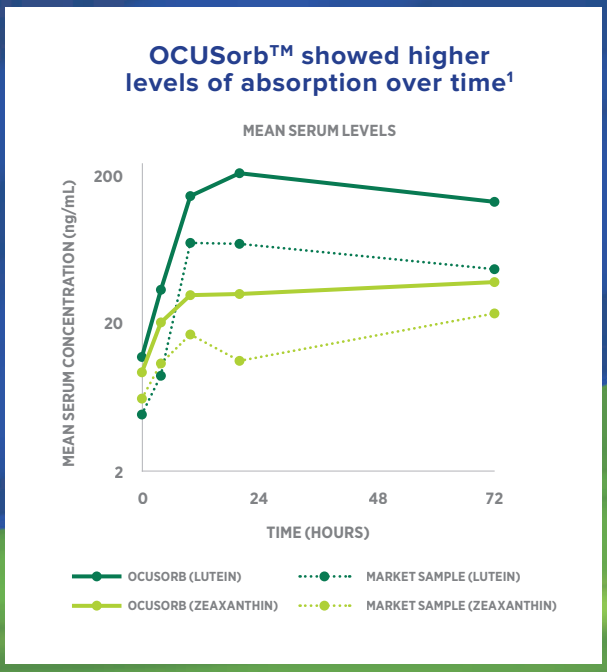

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NEI = National Eye Institute

1. Compared to the market sample. Kotagiri SR, Morde A, Rai D, et al. Ophthalmol Ther. 2022;11(4):1463-1477

‡ Compared to original lutein and zeaxanthin in PreserVision AREDS 2 Soft Gels

*This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

How to Incorporate Nutrition into the Primary Care Practice

BY JEFFREY ANSHEL, OD, FAAO

Nutritional support for visual disorders is a rapidly growing area of eye care. This area can be a specialization of your practice that offers your patients the best of traditional and complementary vision care.

The practitioner must first accept the fact that using nutrition is a valid addition to treating eye disease. While conventional medications certainly have their place, many practices choose to integrate nutrition to support their treatments. This is the core concept of "Integrative Optometry." Many patients prefer the use of natural, effective, and less invasive interventions whenever possible. This process also shows the practice being respectful to patients, listening to their health concerns, and taking their concerns seriously, as well as using good medical judgment.

What Defines a Dietary Supplement

The **Dietary Supplement Health and Education Act** was enacted in 1994 and defines a dietary supplement. However, these products must have this disclaimer: "These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, cure, prevent, or treat any disease." This means that these products are considered foods, not drugs. However, manufacturers are still responsible for safety and effectiveness.

Foods and supplements must both undergo "pre-market notification," whereas drugs need "pre-market approval," both of which are mandated by the FDA. As long as

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a nutrient is considered "Generally Regarded As Safe," a designation that a chemical or substance added to food is considered safe and so is exempted from the usual **Federal Food, Drug, and Cosmetic Act** food additive tolerance requirements, it can be used in a supplement.

There are four general misconceptions regarding vitamins and minerals for patient care:

1. They are completely safe. While that is mostly true, they can be abused and cause dangerous effects if not taken appropriately, just like any over-the-counter item.
2. They are ineffective. The effectiveness of nutrients is much more subtle and long term than it is with drugs, but they are effective nevertheless.
3. They are all the same. Not true, especially when a multiple vitamin is considered. The type, form, and amount of each nutrient can make a major difference in how it works.
4. More is better. This is the most common misconception. Just because a certain amount is effective, it does not mean that 10 times that amount is 10 times more effective!

How to Assess Your Patients' Nutrient Intake

To successfully evaluate patients for nutrient deficiencies, it would be helpful to assess their nutrient intake. That sounds like a daunting task and one best left for nutritionists. However, you can usually get a good sense of their basic diet by asking just a few general questions:

1. How many servings of fruits and vegetables do you eat on a daily basis? (Note: One serving is a ¼ cup or a "handful"). Also, be aware that people will *always* overestimate this amount (and French fries do *not* count as a vegetable). The CDC recommends nine to 13 servings per day.
2. How many times a week do you eat fish (and what kind)? We now realize that smaller, fatty fish (sardines, mackerel, herring, salmon, tuna, etc.) at least three times a week are the best for omega-3 intake.
3. Do you eat baked goods? These contain simple sugars and "bad" carbs, which is worse than eating "bad" cholesterol. Substituting good carbohydrates in vegetables is better.
4. Do you take a full spectrum multiple vitamin/mineral supplement? While we think that eating a "balanced" diet should supply an adequate vitamin intake, it rarely happens, so a supplement is usually required.
5. Do you limit the portion of food that you eat at each meal? Most people eat until the plate or box is empty. Limiting portions can allow you to eat better, more nutrient-dense foods while still losing weight.

Monitor Vitamin Levels in the Blood

Given the national state of optometric licensing, just about every optometrist is allowed to order blood panels. An exact review of vitamin levels in the blood will offer an excellent roadmap of how to proceed in making the appropriate recommendations to your patients. However, knowing a bit of the science and how nutrients are used in supplement form would be helpful. For example, there are eight different forms of vitamin E, and almost all supplements use the tocopherol form and not the tocotrienol form, which has many benefits. Also, vitamin D should be in the D3 form, not D2, which is one-third as effective. Good basic information can be reviewed at the **National Institutes of Health, Office of Dietary Supplements website.**

What to Look For in an Eye Health Supplement

So, what should be considered in a vitamin supplement to help eye health? There are literally dozens of companies in the U.S. alone making hundreds of different products in this category. Patients don't want to be taking pills all day, so try to get as much nutrition as you can in fewer pills. The products should have a valid scientific rationale available for anyone to review as well as a website that puts science first before price and marketing. Any company that promotes making "millions of dollars" by selling its products should be looked at with suspicion. Health goals should be directed toward patient well-being; the income will follow.

The first thing the practitioner should look for is a product that is a good blend and balance of

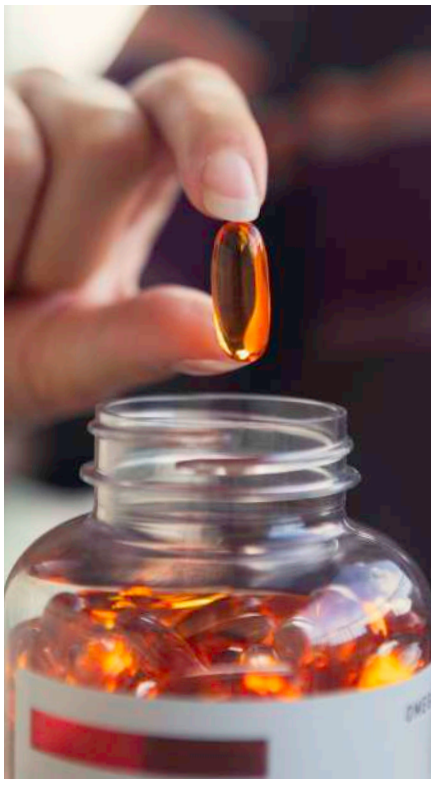


PHOTO CREDIT: Marcus Lindstrom/Getty Images

nutrients that is formulated around the very latest science in nutritional medicine. This is going to take a bit of time considering the number of companies and products that are out there. It's unlikely that the practitioner is going to become a biochemist in the process. Make sure that the scientific rationale for the ingredients is available (usually on their website).

One thing to consider is the form of the pill being offered. Hard-pressed pills are typically found to not break down effectively in the body. A capsule or gel-cap is preferable. Liquids and sprays are also an effective way to get nutritional supplements absorbed.

A full-spectrum supplement should be designed to slow the progression of chronic degenerative disease, including all diseases of the eye. There should be efficacious amounts of properly balanced fat-soluble vitamins, particularly as they relate to the latest vitamin A and vitamin D research. Vitamin A should be in the retinol form, not beta-carotene. It should contain potent amounts of the full spectrum of B vitamins for the proper maintenance of homocysteine, specifically B6, B12, and folic acid. There should also be 400 IUs of the complete spectrum of vitamin E with a balanced mixture of both natural d-alpha tocopherol (not the synthetic form of "dl-alpha tocopherol") and mixed tocopherol oils containing gamma and delta tocopherols and tocotrienols.

Supplemental iron has been linked to heart disease, so a recommended supplement should be iron-free. It should also contain the full army of "job-specific" antioxidants that both prevent free-radical damage as well as neutralize the effects of previous oxidative damage. In addition, there should obviously be efficacious amounts of eye-specific carotenoids: lutein esters (not free lutein) and pure zeaxanthin, to assure proper xanthophyll transport to the retina. It should also contain the spectrum of minerals in their most bioavailable form to ensure proper cellular bioelectrical and enzymatic response.

Learning about nutrition can be a life-long proposition but can be extremely beneficial to you and your patients.

Learn the Basics of Nutrition to Care for Your Patients

Office protocols for approaching the patient should be done in a caring manner. First, diagnose the condition and carefully explain the options to the patient. Then, hand the patient a brochure that fully explains the recommended product. If they decide to purchase it right away, take the bottle to the front desk to dispense as a convenience to the patient. If they want to consider it later, simply let your office staff know (via a routing slip) that the product was discussed with the patient. They can again ask the patient if they wish to make the purchase at the initial visit or at a later time. Either way, the patient knows that it is available and something that can assist in their treatment. A two-week follow-up phone call asking about the status of the nutrient recommendation can increase compliance by up to 50% in many cases. This also demonstrates the doctor's commitment to the welfare of the patient.

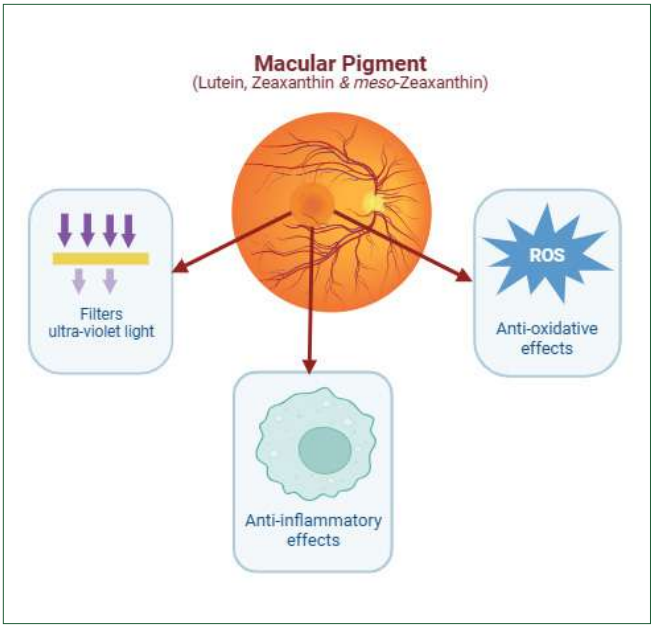
Learning about nutrition can be a life-long proposition but can be extremely beneficial to you and your patients. While we are not biochemists or nutritionists, we should learn some of the basics of nutrition to make intelligent decisions about what to recommend to our patients. If we don't, someone else will. ■

Dr. Jeffrey Anshel is a 1975 graduate of the Illinois College of Optometry. He has written numerous articles and 10 books regarding nutritional influences on vision and computer vision concerns. Dr. Anshel is the principal of Corporate Vision Consulting, where he addresses nutrition and eye health as well as digital eye strain. He lectures internationally to ergonomic professionals and eye care providers on vision health topics. Dr. Anshel is a fellow of the American Academy of Optometry and the founder and past president of the Ocular Wellness and Nutrition Society. He maintains a consulting practice in Kapaa, Hawaii.

Carotenoids In Eye Health

BY EMMANUEL KOFI ADDO, OD, AND PAUL S. BERNSTEIN, MD, PHD

Carotenoids are natural pigments present abundantly in plants and in microorganisms such as fungi and bacteria. Carotenoids exist in two forms based on their chemical structure, the oxygenated xanthophylls (i.e., lutein, zeaxanthin, and *meso*-zeaxanthin) and the non-oxygenated carotenes (i.e., *β*-carotene, *β*-cryptoxanthin, *α*-carotene, and lycopene).



These micronutrients all have a core chemical formula of $C_{40}H_{56}O_{[0-2]}$ with a conjugated double-bond backbone.[1, 2] Over 700 carotenoids exist in nature, where they are responsible for the bright coloration of many fruits and vegetables. About 50 of these carotenoids are present in the diet of humans, with approximately 10 to 15 detectable in the human serum.[3, 4] Of these, only lutein, zeaxanthin, and *meso*-zeaxanthin, which is derived from lutein, uniquely localize in the macula of the human eye. These account for the yellow spot in the *macula lutea,* the central portion of the eye responsible for detailed spatial vision, and they are collectively referred to as the macular pigment.[5-7] Like other animals, humans lack the required enzymes to synthesize carotenoids *de novo*. Therefore, carotenoids must be obtained exclusively by ingesting green leafy vegetables, orange-yellow fruits and vegetables, egg yolk, and fortified dairy products or by supplementation.[8, 9] Currently, no recommended daily allowance exists for carotenoids. However, the U.S. Food and Drug Administration considers carotenoids as generally recognized as safe for human consumption, and the European Food Safety Authority allows doses of up to 1 mg/kg body weight per day day of lutein and 0.75 mg/kg body weight/day of zeaxanthin.[10]

Macular Pigment Distribution in the Eye

Lutein is the predominant carotenoid in vision-related tissues such as the eye and the brain.[11] Macular pigment's highest concentrations are found in the macula of the retina, especially the Henle's fiber layer, where levels are significantly elevated relative to the serum and other tissues.[12, 13] Recent findings from our laboratory show that the zeaxanthins (zeaxanthin and meso-zeaxanthin) highly localize to the human fovea, while lutein is widely diffused across the macula at a much lower concentration relative to the zeaxanthins, suggesting that the zeaxanthins are more critical than lutein as the foveal macular pigment.[7]

Lutein, zeaxanthin, and meso-zeaxanthin, which is derived from lutein, uniquely localize in the macula of the human eye.

Biological Functions

The high concentration of macular pigment in the primate fovea implies a potential physiological function and prompts inquiry into why the eye would go to such lengths to concentrate macular pigment in the retina. Outlined below are the known functions of macular pigment in the eye.

LIGHT FILTER

Macular pigment has high light absorptivity due to its polyene chain backbone with its numerous conjugated double bonds. The yellow macular pigment efficiently filters and attenuates short-wave-

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- Reduced eye strain & improved visual performance

BETTER VISUAL PERFORMANCE

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- Faster reaction time for sports and everyday activities
- Improved ability to perceive fine details

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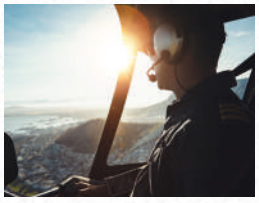
Sports Performance


Visually Demanding Careers


Eye Strain Complaints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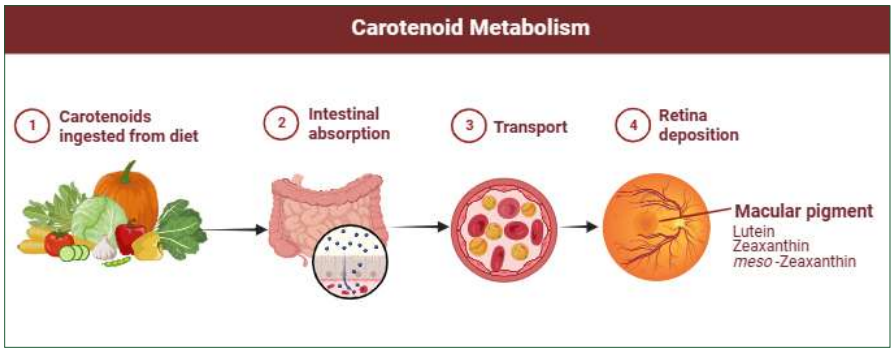
length visible light in the blue range before it reaches the delicate distal structures, including the photoreceptors, the retinal pigment epithelial (RPE), and the underlying choriocapillaris. The decrease in light intensity abates oxidative stress and enhances visual performance by attenuating chromatic aberration, reducing luminance and blue haze. Studies report a direct positive relationship between macular pigment status and visual acuity, contrast sensitivity, photostress recovery, and glare reduction.[14-16]

ANTIOXIDANT PROPERTY

Macular pigment accumulates in a region of the eye that is highly susceptible to oxidative stress due to the focused light and high oxygen environment, which can generate reactive oxygen species (ROS).[7] ROS can potentially cause irreversible damage to lipid membranes, which can lead to degenerative eye diseases. Due to the macular pigment's chemical structure, it functions efficiently and effectively to quench the dangerous singlet oxygen and free radicals by interrupting the chain of oxidative reactions, preventing oxidative damage to retinal cells.[17, 18] This antioxidant capacity helps preserve the integrity of retinal tissues and may contribute to preventing age-related macular degeneration (AMD) and other ocular disorders linked to oxidative stress[19].

ANTI-INFLAMMATORY PROPERTIES

Beyond their antioxidant role, macular pigment exhibits significant anti-inflammatory effects.[20] Inflammation plays a pivotal role in the development and progression of various eye diseases. Macular pigment's anti-inflammatory properties are thought to arise from their ability to modulate the expression of genes related to inflammation and cytokine production.[21, 22] By doing so, they help mitigate the inflammatory response within ocular tissues. Additionally, these carotenoids have been linked to the reduction of factor D, an enzyme associated with the alternative complement activation pathway.[23] By influencing this pathway, macular pigment may contribute to regulating systemic inflammation, which could positively impact ocular health.



Carotenoid Metabolism

All carotenoids are highly hydrophobic lipid molecules that are metabolically active. These pigments are often present in food matrices as fatty acid esters that are cleaved in the gut and incorporated into lipid micelles. Intestinal cells' surface proteins aid in the uptake and transport of these carotenoids to the lymphatic and portal circulations within the chylomicron fraction.[24] Among carotenoids, hydrophobic ones such as lycopene and β-carotene are transported on low-density lipoprotein, whereas more hydrophilic xanthophyll carotenoids such as macular pigment are primarily carried by high-density lipoprotein.[25] Proteins expressed on RPE cells facilitate macular pigment uptake into the retina.[26] Macular pigment's unique localization in the retina suggests the involvement of specific binding proteins. Carotenoid-binding proteins in the human macula, including glutathione S-transferase Pi 1[27] and steroidogenic acute regulatory domain protein 3,[28] play crucial roles in the specific delivery and stabilization of zeaxanthin and lutein in the retina, respectively. Also, the reduced cleavage activity of endogenous BCO2 enzymes in the human retina ensures a sustained high level of macular carotenoids.[29]

Macular Pigment Measurement

Diverse techniques exist for measuring macular pigment across different body components. These measurements collectively contribute to our understanding of the significance of macular pigment in ocular and overall health. Herein, we highlight the commonly used devices for serum, eyes, and skin carotenoid assessments.

MEASUREMENT OF MACULAR PIGMENT IN THE SERUM

Serum measurements of macular pigment involve analyzing blood samples for carotenoid concentrations. High-performance liquid chromatography is a widely used

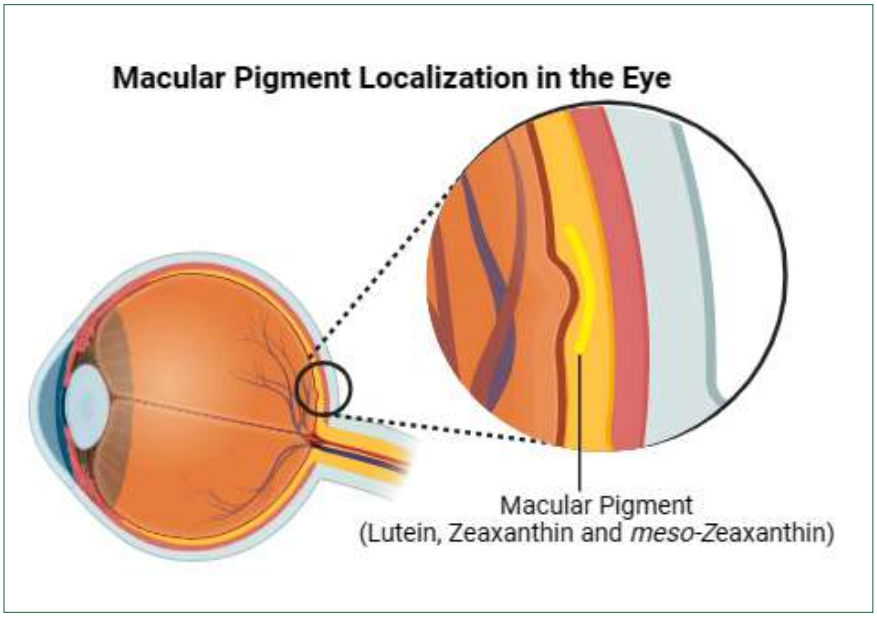
method that is the gold standard for quantifying carotenoids in the blood.[5] While serum concentrations may not directly mirror macular pigment levels, they provide insights into carotenoid intake and bioavailability and their subsequent distribution to various tissues. Serum macular pigment measurements are valuable indicators of overall carotenoid status and may offer information about macular health, as they are strongly correlated.[30]

MEASUREMENT OF MACULAR PIGMENT IN THE EYES

Direct measurement involves techniques such as heterochromatic flicker photometry (HFP) and autofluorescence imaging (AFI). HFP is a psychophysical method that assesses the relative intensities of blue and green lights required to minimize a flickering stimulus projected onto the fovea to determine macular pigment optical density (MPOD).[31] AFI is an objective optical method that measures the autofluorescence emitted by fluorophores (primarily lipofuscin) in the RPE upon excitation by diode lasers (i.e., blue and green laser light). Macular pigment, located anterior to the RPE, attenuates lipofuscin's autofluorescence if the excitation wavelength falls within the macular pigment's absorption spectrum, leading to an area of diminished fluorescence. This yields information about MPOD and macular pigment optical volume (MPOV), a measure of total macular pigment in the assessed region.[32] These methods offer quantitative assessments of macular pigment levels and aid in evaluating their potential impact on vision and eye health.

MEASUREMENT OF TOTAL CAROTENOIDS IN THE SKIN

Measuring macular pigment and other carotenoids in the skin involves objective non-invasive optical techniques, such as resonance Raman spectroscopy and reflection spectroscopy, that provide insights into the body's overall carotenoid status.[33, 34] Both techniques estimate total carotenoid levels by assessing the amount of light obtained from the skin after exposure to a special light source. These methods correlate well with macular pigment levels in the eye and serum,[30, 34-40] and serve as a surrogate biomarker for estimating carotenoid intake and its potential ocular benefits.



Macular Pigment Status and Eye Health

VISUAL PERFORMANCE

Macular pigment offers substantial benefits across various aspects of visual performance throughout the human life span. Epidemiological and randomized controlled trials consistently report that macular pigment enhances contrast sensitivity and visual acuity and reduces glare.[14-16] This improvement is attributed to the pigment's light-filtering properties in the central fovea. Also, its positive influence on visual performance indirectly contributes to improved quality of life and independence for individuals, as it helps maintain visual functions necessary for daily activities such as reading, driving, and recognizing faces.

AGE-RELATED MACULAR DEGENERATION

There is strong evidence suggesting that macular pigment is protective against AMD development and progression.[2] Its ability to filter and absorb harmful short wavelength light reduces the potential for phototoxicity and oxidative stress in retinal cells, which is crucial to prevent and mitigate oxidative damage contributing to AMD progression.[22] Moreover, the macular pigment's anti-inflammatory properties and capacity to neutralize free radicals offer a protective shield against retinal inflammation and degeneration, underscoring its significance as a natural defense against the development and advancement of AMD. Several studies have shown that higher macular pigment status

is associated with a reduced risk of AMD and lower levels increase vulnerability to oxidative damage and inflammatory processes implicated in AMD pathogenesis.[41-43] The Age-Related Eye Disease Study 2 (AREDS2), which began in 2006, found that 10 mg/day of lutein and 2 mg/day of zeaxanthin were a safer and more effective substitute for the 25 mg/day of β-carotene in the original AREDS formula, which had been linked to increased risk of lung cancer in current and former smokers.[19] A five-year follow-up of the AREDS2 trial revealed that over 10 years, the lutein/zeaxanthin group exhibited a 20% lower risk of advancing to late AMD compared to the β-carotene group.[44] Thus, monitoring and optimizing macular pigment status through dietary intake or supplementation can contribute to AMD prevention and management.

RETINOPATHY OF PREMATURITY (ROP)

Macular pigment potentially mitigates the development and severity of ROP. Its antioxidative and anti-inflammatory properties counteract oxidative stress and inflammation, key factors in ROP development.[17, 18] Augmenting macular pigment status, especially in premature infants with lower levels, could potentially mitigate ROP risk by providing enhanced protection against light-induced damage and retinal stress.[39] We recently reported that prenatal supplementation of lutein or zeaxanthin in a mouse model of ROP significantly inhibited oxygen-induced retinopathy.[45] Unlike full-term babies, macular pigment is undetectable in premature babies due to foveal immaturity and oxidative stress. Trials of postnatal macular pigment supplementation to prevent ROP were inconclusive, however, and we suspect the timing of supplementation might be the possible reason.[39] We intend to study prenatal macular pigment supplementation in high-risk mothers to determine its potential to prevent ROP because we have recently shown that adding an AREDS2 dose of lutein and zeaxanthin to prenatal vitamins is safe and well tolerated and effectively increases the mother and her child's ocular and systemic carotenoid status in low-risk pregnancies.[46, 47]

Macular pigment is protective of the visual system throughout the life span. Therefore, measures to enhance and sustain macular pigment levels through diet or supplementation for optimal visual performance and ocular health should be promoted. Incorporating non-invasive carotenoid assessment into routine eye care examinations could identify individuals at risk for future age-related eye diseases and facilitate early interventions. ■

Dr. Emmanuel Kofi Addo, OD, is currently a fifth-year PhD candidate at the Bernstein Laboratory, located at the Moran Eye Center, University of Utah Health, Salt Lake City, Utah. He received his optometry training at Kwame Nkrumah University of Science and Technology, Kumasi, Ghana. Dr. Addo's research explores how prenatal carotenoid supplementation impacts the ocular and systemic carotenoid levels of both mothers and their children in the Lutein and Zeaxanthin in Pregnancy (L-ZIP) study. Additionally, he examines whether awareness of genetic risk for AMD influences individuals to adopt healthier lifestyles, potentially reducing AMD incidence in later life, through the Moran AMD Genetic Testing and Assessment (MAGENTA) study. Dr. Emmanuel is a student member of esteemed professional organizations such as the American Academy of Optometry, the Association for Research in Vision and Ophthalmology, and the Brain and Ocular Nutrition Group. His work has been presented on international platforms and garnered well-deserved recognition.

Dr. Paul S. Bernstein, MD, PhD, joined the faculty of the Moran Eye Center of the University of Utah in 1995 where he currently divides his time equally between clinical and basic science retina research and a clinical practice devoted to medical and surgical treatment of diseases of the retina and vitreous with special emphasis on macular and retinal degenerations. He is the Val A. and Edith D. Green Presidential Professor of Ophthalmology and Visual Sciences. Dr. Bernstein did his undergraduate, MD, and PhD training at Harvard University, his ophthalmology residency at Jules Stein Eye Institute of UCLA, and his vitreoretinal fellowship at Massachusetts Eye & Ear Infirmary. Dr. Bernstein's current research interests focus on the biochemistry and biophysics of nutritional interventions against inherited and acquired ocular disorders. Dr. Bernstein has authored over 200 peer-reviewed research articles and reviews, and he has served as a reviewer for numerous journals, foundations, and institutes. Dr. Bernstein currently serves as the Vice Chair for Research at the Moran Eye Center, and he was 2016-2017 Vice President of ARVO.

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Omega-3 Fatty Acids and Ocular Health

BY WILLIAM S. HARRIS, PHD, FAHA, FASN

There are obviously multiple nutrients that impact visual health.[1] For much of the Third World, vitamin A deficiency is a major cause of childhood blindness. For eye diseases that manifest later in life – cataracts, age-related macular degeneration (AMD), glaucoma, dry eye disease (DED), and diabetic retinopathy – chronic poor nutrition is believed to play a facilitating if not causal role. One of the nutrients that has attracted much attention in ocular health is the long-chain polyunsaturated fatty acids (LC-PUFAs) in the omega-3 family, most notably docosahexaenoic acid (DHA). Since the retina is one of the most DHA-rich tissues in the body,[2] it would be natural to explore why this might be and how long-term DHA insufficiency might affect vision. One of the earliest discoveries in this area was that DHA deficiency resulted in diminished visual acuity in infants,[3] but the extent to which this is due to low levels of DHA in the retina, the optic nerve, or the visual cortex is not clear. As the eye is essentially an extension of the central nervous system, deficiency in one component suggests that DHA levels will be suboptimal in all. Here are the roles that DHA may play in the five visual disorders of adulthood outlined above.

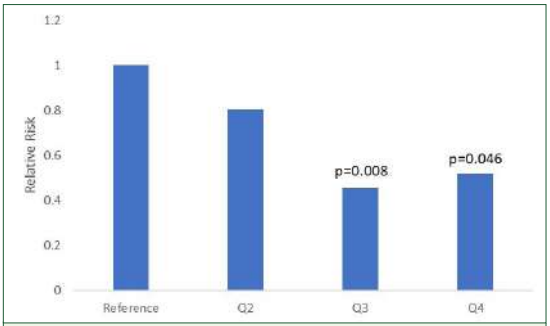

Figure 1. Relative risk for developing early age-related macular degeneration by quartile of plasma phospholipid DHA levels. Adjusted for age, race, sex, cholesterol, triglycerides, smoking, BMI, statin use, and the Healthy Eating Index. P for trend = 0.045. (Data from Karger et al.[8])

Cataracts

As we age, the lens of the eye can begin to become opaque. This is often seen as a normal consequence of aging, but a variety of conditions and/or behaviors may accelerate the disease. Among these are diabetes, certain drugs, UV radiation, smoking, alcohol use, and genetic propensities (i.e., a family history of cataracts). There has been relatively little attention paid to how omega-3 might affect cataract development, however, two observational studies, one from the Nurses Health Study[4] and another from the Blue Mountains Eye Study,[5] both found that higher intakes of fish and n-3 LC-PUFAs were associated with significantly lower risk for developing cataracts.

Age-related Macular Degeneration (AMD)

AMD is another disorder affecting mostly older individuals wherein the macula (the center of the retina, where visual images are most sharply focused) begins to degrade. This results in a gradual loss of central vision, forcing people to rely more and more on peripheral vision to see the world around them. For many years, there have been suggestions that higher omega-3 levels in the retina (which is the most DHA-rich tissue in the body[6]) might protect against the loss of macular function, coming largely from studies correlating reported fish intake with the development of AMD. An example is again from two prospective cohort studies from Harvard, the Nurses Health Study and the Health Professionals Follow-up Study, where estimated EPA (eicosapentaenoic acid) +DHA intake from food frequency questionnaires was compared with the risk for developing either intermediate or advanced AMD.[7] This study found that higher intakes of primarily DHA were significantly associated with lower risk for intermediate AMD but not for advanced AMD. A more recent study from the Multi-Ethnic Atherosclerosis Study (MESA, which followed 3,772 AMD-free individuals for 10-12 years) found a significant inverse association between plasma phospholipid DHA levels and risk for early AMD (Figure 1).[8] This relationship remained significant even after including a measure of "healthy lifestyle" (the Healthy Eating Index) in the model. These findings supported previous work by Merle et

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al. who reported that erythrocyte EPA+DHA levels (i.e., the omega-3 Index) was inversely associated with the development of neovascular AMD.[9] In the largest randomized trial to examine the effects of supplemental EPA+DHA on the development of AMD, Christen et al. found that providing 840 milligrams per day of EPA+DHA for a median of 5.3 years, reduced the incidence of AMD by 27% (p=0.047) compared with placebo.[10] Thus, it appears that higher omega-3 status can slow the initial development of AMD, but it may not prevent progression of intermediate to late AMD.

Fish is the best source of omega-3's. The nutrient data below is provided by the U.S. Department of Agriculture.

TYPE OF FISH (3 OZ. SERVING)	OMEGA-3 CONTENT (DHA + EPA)
Mackerel	2.0 grams
Salmon (Farmed, Atlantic)	1.7 grams
Herring (Atlantic)	1.3 grams
Anchovy	1.2 grams
Salmon (Wild, Atlantic)	1.2 grams
Whitefish	1.1 grams
Tuna (Bluefin)	1.0 grams
Halibut (Greenland)	0.8 grams
Sardines (Atlantic, Canned in Oil)	0.8 grams
Tuna (Albacore, Canned In Water)	0.7 grams
Bluefish	0.7 grams
Striped Bass	0.6 grams
Rainbow Trout (Wild)	0.5 grams
Tuna (Light, Canned In Water)	0.5 grams

Note: If you are pregnant or a child under 11 years of age, it is imperative to be mindful of the mercury content of certain fish. Avoiding larger species of fish that mainly eat other fish is recommended for pregnant women and children due to the higher mercury content of these fish.

Glaucoma

Glaucoma is another eye disease in which fluid pressure builds up inside the eyeball to the point where it damages the optic nerve. Although relatively little research has focused on the relationship between omega-3 and glaucoma, a small study by Acar et al. did find a strong inverse relationship between the severity of glaucoma and RBC DHA levels.[11] An intervention study in 105 young, normotensive adults found that ~1.5 g of EPA+DHA per day reduced intraocular pressure by 8% compared with placebo after three months of treatment.[12] Much more work is needed to follow up on these encouraging, early findings.

Dry Eye Disease

Of all the adult eye conditions, the most studied is the role of EPA+DHA in DED. The theoretical basis for such investigations is the well-known anti-inflammatory effect of the omega-3 LC-PUFAs.[13] Observational studies led the way with a report from the Women's Health Study, where women in the highest quintile of EPA+DHA intake were 17% less likely to report having DED.[14] Multiple randomized trials followed. Two recent meta-analyses have found evidence for a benefit in DED,[15, 16] but bigger and longer-term studies were needed. Such a trial was published in 2023 by Bhargava et al.,[17] specifically in users of "visual display terminals (VDT)" (i.e., computer screens). They randomized 950 individuals to either 2.4 g of EPA+DHA daily vs. an olive oil placebo and followed them for up to six months. They also measured the Omega-3 Index pre and post to both document compliance and to be able to compare outcomes based on changes in blood EPA+DHA levels regardless of randomization group. They concluded that, "omega-3 fatty acid supplements are effective in relieving dry eye symptoms and improving dry eye indices in symptomatic VDT users in comparison to olive oil placebo. The benefit seems to be more marked in patients with low omega-3 index." In a 2022 study comparing eye drops containing EPA+DHA with an over-the-counter product used to treat DED (2% povidone), tear break-up time and ocular surface disease index scores improved similarly on both products. Considering the safety of omega-3 LC-PUFAs, these findings strongly support the use of such supplements in DED.

Diabetic Retinopathy (DR)

Patients with poorly controlled type 2 diabetes mellitus (T2DM) experience widespread small vessel damage that is particularly devastating for retinal health. Again, due to the known benefits of omega-3 LC-PUFAs on both inflammation and vascular health,[18] a potential benefit in reducing risk for DR would not be unexpected. Such a relationship was supported by a major report from the PREDIMED cohort in which an intake of EPA+DHA of less than 500 mg per day (based on data from a validated food frequency questionnaire) was significantly

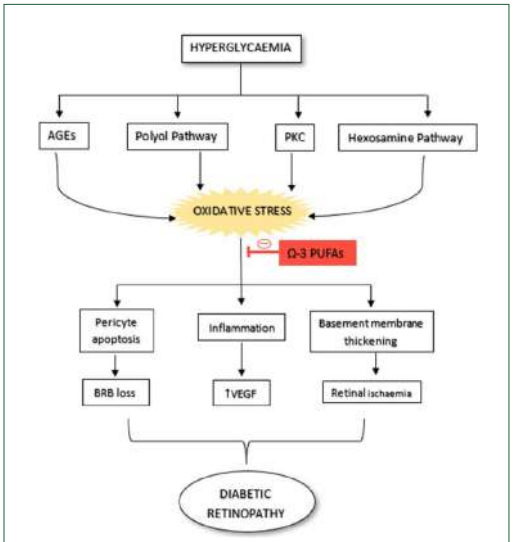
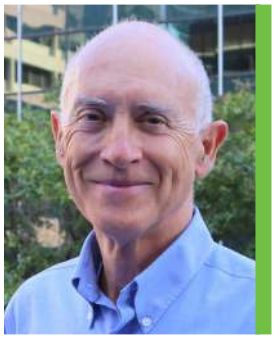


Figure 2. Potential mechanisms by which omega-3 LC-PUFAs are protective against diabetic retinopathy via their antioxidant properties. Figure from Georgiou et al.[21]

associated with an increased risk for incident DR over a six-year follow-up period in 3,482 patients with T2DM.[19] In a multi-variable adjusted model, the odds of developing DR were 59% lower (p=0.002) in T2DM patients who reported eating at least two servings per week of oily fish compared to those not meeting this criterion. This dietary intake-based finding was confirmed in 2023 by a biomarker-based study in 1,356 patients with T2DM in which blood DHA levels were inversely related to both the presence and the severity of DR.[20] *In vitro* and animal studies have identified anti-oxidative mechanisms that could explain this effect (Figure 2).

Increasing the intake, and thus the tissue levels, of omega-3 LC-PUFA has many benefits in terms of eye health. From the front (cornea) to the back (retina) of the eye, optimal levels of DHA in particular appear to slow the development of multiple adult-onset ocular diseases. Achieving higher (e.g., >8%) omega-3 Index levels, which has been shown to be protective in multiple settings,[22-24] should be included in any strategy to reduce risk for visual disorders. ■



Dr. William S. Harris, PhD, FAHA, FASN, is a professor in the Department of Internal Medicine, Sanford School of Medicine, University of South Dakota; and president, Fatty Acid Research Institute, Sioux Falls, S.D. He holds a PhD in Nutritional Biochemistry from the University of Minnesota. Since 1980, his research has focused on omega-3 fatty acids. He has been the principal investigator on five omega-3-related NIH grants and has published more than 340 papers on omega-3 fatty acids. In 2004, he co-developed the "Omega-3 Index," a blood test to assess EPA+DHA status that can be performed on dried blood spots. In 2009, he formed OmegaQuant, LLC, to offer the test to researchers, health care providers, and consumers. In 2020, he established the Fatty Acid Research Institute. His scientific productivity was ranked among the top 2% in a recent survey of scientists worldwide.

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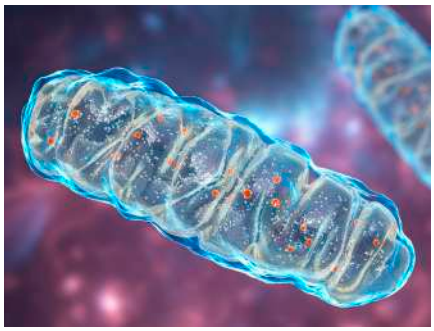
Mitochondria: Why Supporting Mitochondrial Health is Important to Eye Health

BY JULIE POTEET, OD, CNS, FOWNS, AND NEDA GIOIA, OD, CNS, FOWNS

Mitochondria are the energy powerhouses of every cell in the body as they produce most of the energy or adenosine triphosphate (ATP) required by the cell. The mitochondria have their own genome (mtDNA) that is replicated independently of the host genome and is more susceptible to damage than nuclear DNA. Unfortunately, our modern diet and lifestyle compromise our mitochondria, which results in suboptimal function of the eye, brain, and other organs.



Mitochondrial Dysfunction in Aging

When mitochondria begin to function suboptimally, tissues start to break down. Here is how our modern lifestyle and aging affect mitochondrial function of every cell in the body.

Aging correlates with mitochondrial dysfunction. As organisms grow older, their mitochondria become less efficient at producing energy, which can lead to a decrease in overall cellular function. Excessive oxidative stress, often associated with aging, can damage mitochondrial DNA and proteins. Chronic diseases of the eye such as macular degeneration, glaucoma, and diabetic retinopathy all have excessive oxidative stress as a common underlying disease process.

- **Mitochondrial Reactive Oxygen Species (ROS):** ROS are natural byproducts of energy production. Mitochondria are the greatest source of ROS. Low levels of ROS are necessary, but when ROS become excessive, they can damage mitochondrial DNA and proteins, contributing to cellular aging.[1]
- **Mitophagy:** Damaged or dysfunctional mitochondria are selectively removed by autophagy. Well-regulated autophagy is vital to the health of the cell. Maintaining a balance in this process is crucial for cellular health, and disruptions accelerate aging and inflammation.[1]
- **Sirtuins:** These are a class of proteins that play a vital role in regulating mitochondrial function and cellular longevity. They help repair and maintain mitochondria. It has been shown that proper lifestyle, including physical activity and diet, can influence health span via increasing the level of sirtuins.[1]
- **Caloric Restriction:** This can extend life span by enhancing mitochondrial function and reducing oxidative stress. Fasting and caloric restriction activate sirtuins and promote mitochondrial health.[1]
- **Therapeutic Potential:** Improving mitochondrial function with therapies such as those that activate sirtuins could hold promise as potential anti-aging therapies.[1]

The retina is highly predisposed to oxidative stress due to intense blood flow, high metabolic rate, the presence of mitochondria-rich cells, high concentrations of easily oxidized polyunsaturated fatty acids in membranes, and prolonged exposure to light. Since ROS are primarily produced by the respiratory chain of the mitochondria, mitochondria are major sites of oxidative stress. It is important to note that the retina has more mitochondria than any other tissue and ages rapidly.[2]

Ocular mitochondria are the source of antioxidant and protein repair systems but are also, as stated above, the main endogenous source of ROS. Oxidatively damaged mitochondria are unable to maintain redox balance and to repair damaged proteins. Furthermore, ROS produced by injured mitochondria induce the autophagy/mitophagy process. In the eye, autophagy plays a critical role in maintaining normal cellular function, and alterations in the autophagy process contribute to age-related ocular disease.

PHOTO CREDIT: KATERYNA KON/SCIENCE PHOTO LIBRARY/Getty Images

CATARACTS:

Mitochondria are abundant in the lens. Aged lens cells are high in ROS and damaged mitochondria and are characterized by lower levels of antioxidants such as glutathione.[3] Glutathione and mitochondria antioxidant enzymes control redox balance in the lens. Autophagy and mitophagy processes attempt to restore lens homeostasis, but their failings often result in more ROS, oxidation, and finally cataract formation.

GLAUCOMA:

Mitochondrial stress and nitro-oxidative stress are essential in the onset and progression of primary open-angle glaucoma (POAG).[4] Mitochondrial dysfunction can also be secondary to glaucomatous pathogenic factors, such as elevated mechanic stress and insufficient retinal perfusion, which consequently leads to diminished oxidative substrates, disrupted mitochondrial biogenesis, and insults to the electron transport chain. In this way, mitochondrial dysfunction contributes to reduced energy availability, an increased net production of ROS, the accumulation of damaged mitochondria, and the activation of apoptosis.[5, 6, 7, 8, 9]

MACULAR DEGENERATION:

Aged photoreceptors, choriocapillaris, and retinal pigment epithelium (RPE) cells are subjected to intense oxidative insult because of their constant exposure to visible light, daily phagocytosis of photoreceptor outer segments, high local oxygen concentrations, presence of intracellular photosensitizers, and choroidal blood photoactive compounds.[2, 10] Additionally, damaged RPE cells present inadequate systems of antioxidant defense and mitochondrial DNA repair.[2]

LIFESTYLE FACTORS THAT SUPPORT MITOCHONDRIAL FUNCTION

Exercise: Endurance exercise training has long been appreciated to enhance mitochondrial function. High intensity interval training and weight training are now also recognized as ways to boost mitochondrial function.[24]

Cold Therapy: Exposure to quick bursts of cold temperatures such as being outdoors in the cold for 20-30 seconds or in a cold shower will boost mitochondrial production through a process called hormesis.[25] (What doesn't kill us makes us stronger!)

Heat Therapy: Like cold therapy, heat therapy such as saunas increases the number and function of mitochondria without exercise.[26]

Mindfulness Meditation: Regular mindfulness meditation can turn on genes that support healthy mitochondria. In a 2013 study at the Massachusetts General Hospital in Boston, mindfulness meditation effectively changed the gene profiles of subjects.[27] The healthy genes had the following effects: improved mitochondrial function, reduced blood sugar, increased insulin, and stabilized DNA that slows aging. At the same time, mindfulness turned off genes that cause inflammation.

MEDITERRANEAN DIET AND MITOCHONDRIA

Diet has been associated with oxidative stress and inflammation. Mitochondria can perceive inflammatory signals, and they are among the first organelles affected by systemic inflammation.[21] Several studies have shown that high-quality diets, such as the Mediterranean Diet, were associated with lower oxidative stress levels and so a lower incidence of diseases.[22] Different experimental models show that components of the Mediterranean Diet, including polyphenols, plant-derived compounds, and polyunsaturated fatty acids, can improve mitochondrial metabolism, biogenesis, and antioxidant capacity.[23]

NUTRIENTS THAT HELP SUPPORT MITOCHONDRIAL HEALTH AND THE EYE

Coenzyme Q10 (CoQ10): CoQ10 is a vital component of the electron transport chain in mitochondria, where it plays a crucial role in ATP production. It also acts as an antioxidant, helping to protect mitochondria from oxidative stress.[15]	**Vitamin B Complex:** B vitamins, including B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine), and B12 (cobalamin), are essential for various metabolic reactions, including those within mitochondria.[19]
Antioxidants: Antioxidants such as vitamins C and E, as well as glutathione, help protect mitochondria from oxidative damage and maintain their function.[19]	**Alpha-Lipoic Acid (ALA):** ALA is an antioxidant that helps protect mitochondria from oxidative damage. It also plays a role in mitochondrial energy metabolism.[17]
Omega-3 Fatty Acid: Omega-3 fatty acids, particularly docosahexaenoic acid (DHA), may support mitochondrial function and reduce oxidative stress in cells.[20]	**Magnesium:** Magnesium is a cofactor for many enzymes involved in ATP production. It is essential for proper mitochondrial function and energy metabolism.[18]

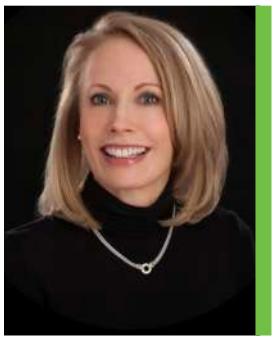
L-Carnitine: L-Carnitine is involved in the transport of fatty acids into mitochondria for energy production. It supports mitochondrial function, especially in cells that rely on fatty acid metabolism for energy.[16]

DIABETIC RETINOPATHY:

Oxidative stress underlies the pathogenesis of diabetic retinopathy.[2, 11] Inflammatory processes also contribute to the development of diabetic retinopathy, and thus it is considered a low-grade inflammatory disease.[2, 12] Chronic inflammation is both a driver of and cause of mitochondrial dysfunction.

DRY EYE:

Dry eye is an inflammatory disease. ROS is elevated in dry eye disease. Numerous factors can cause an elevation of ROS, but mitochondria are the number one producers of ROS in humans, especially as the mitochondria become less functional with age. Recent studies have shown that substances that act as antioxidants such as melatonin have the ability to improve dry eye disease by protecting corneal epithelial cell viability and inhibiting apoptosis from oxidative damage.[13, 14] ■



Dr. Julie Poteet, OD, MS, CNS, FOWNS, graduated from The New England College of Optometry and then completed a residency in primary care and ocular disease at the VA Medical System in Boston. At the VA, Dr. Poteet became interested in why some veterans seemed to age so differently from their peers and began questioning what lifestyle factors have the greatest impact on health and vitality. She then went on to complete a Master of Science in Human Nutrition and Functional Medicine. After earning her Master's Degree, she then completed the requirements to become a Certified Nutrition Specialist in 2015, becoming one of the first ODs to attain CNS certification. Dr. Poteet served as Vice President of the Ocular Wellness & Nutrition Society (OWNS) for six years under her mentor Dr. Stuart Richer, and she served as president of OWNS for three years. She has lectured extensively on the microbiome and immune system dysfunction. She works in Atlanta, where her office is a Macular Degeneration Center of Excellence. She is a member of the American Nutrition Association, formerly the American College of Nutrition. Dr. Poteet is passionate about carrying on the legacy of her mentor, Dr. Stuart Richer, whose mantra "repair the roof before it starts raining" is an excellent metaphor for using lifestyle and nutrition to mitigate the course of disease.

Dr. Neda Gioia, OD, CNS, FOWNS, is the founder and owner of Integrative Vision, an optometry practice in New Jersey with a distinct focus on nutritional interventions and functional medicine strategies for enhancing eye health. Her personal experience with nutrition inspired her to pursue a formal education in the field. Following her graduation from SUNY Optometry in 2006, she has earned functional medicine certifications and became a Certified Nutrition Specialist through the American Nutrition Association. She now serves as president of the Ocular Wellness and Nutrition Society. She also serves on the Women in Optometry board. Dr. Gioia is continuing her education path with the Institute for Functional Medicine and innovates with service-driven solutions such as her **SEEHealth** programs and **Eye Exam Plus.** Her enduring objective is to heal, educate, and empower both patients and fellow practitioners to integrate nutrition within health care practices in eye care.

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The Gastrointestinal Microbiome: A Vital Human Organ

BY JULIE POTEET, OD, MS, CNS, FOWNS

"The hundred trillion bacteria in the body of an adult human contain about four million distinct bacterial genes, with more than 95% of them located in the large intestine. Since most of these genes encode for enzymes and structural proteins that influence the functioning of mammalian cells, 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." (Galland L. Gut Microbiome and Brain. J Med Food 2014)

The health of the eye is linked to the health of the intestine. It is now well established in the literature that our lifetime partners, the over one hundred trillion bacteria that live within us and on us, have a significant impact on our health by influencing the function of our immune systems. Chronic inflammation, the root of the chronic diseases of aging, is largely influenced by our lifetime partners that comprise the human microbiome. In fact, a dysfunctional gut is one of the biggest drivers of chronic inflammation.

Several ocular diseases such as dry eye disease, diabetic retinopathy, and macular degeneration are linked to the gut microbiome.

'All Disease Begins in the Gut' — Hippocrates

With 95% of our microbiome located in the large intestine, emerging studies are revealing a diet-gut-eye axis where several ocular diseases such as dry eye disease, diabetic retinopathy, and macular degeneration are linked to the gut microbiome. 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 Gastrointestinal Microbiome at a Glance:

- **Contains one hundred trillion viable microorganisms,** which is 10 times the number of cells in the human body.
- **Over 1,000 different species,** a mutually beneficial relationship.
- **Weighing 1-1.5 kg,** can be considered an additional human organ rivaling the liver for the number of biochemical reactions in which it participates.
- **While the human genome consists of approximately 23,000 genes,** the gut microbiome encodes more than three million genes and produces thousands of metabolites.
- **Most important component of the gastrointestinal (GIT) microflora is the colonic microflora** (far outweighing those found elsewhere), where bacterial species can be divided into potentially harmful or health-promoting groups.
- **Modulates the immune system:** shifts T-helper cell balance toward Th1, resulting in decreased production of IgE and eosinophils, dampened hypersensitivity reactions and intestinal inflammation, greater oral tolerance, and prevention of atopic disease.
- **Enhances GIT** motility and function.
- **Improved digestion and nutrient absorption** (approx. 10% of daily E needs), salvages energy from unabsorbed carbohydrates in the colon to form short chain fatty acids (SCFAs), improves the absorption of calcium, magnesium, and trace minerals.
- **Produces vitamins** in the B group and K groups.
- **Xenobiotic metabolism:** important for absorption and proper functioning of phytoestrogens, lignans, flavonoids, and some medicinal herbs.
- **Colonization resistance:** the protection against colonization of the intestinal tract with potentially pathogenic bacteria afforded by the intestinal flora.
- **Weight management:** microflora play a vital role in energy homeostasis, and obese microbiota has an increased capacity to harvest energy from the diet.

Dysbiosis

Bacterial species in the gut microbiome can be divided into potentially harmful or health-promoting groups. 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.[1] In his book *Human Microbiome and Dysbiosis in Clinical Disease*, Dr. Alex Vasquez describes the three most important consequences of an insufficiency of beneficial bacteria in the gut, or dysbiosis:[2]

1. Lack of immunotolerance and increased systemic inflammation.
2. Additional inflammation induced by pro-inflammatory bacteria and increased absorption of antigens.
3. Direct absorption of bacteria, microbial DNA, and pro-inflammatory structures such as lipopolysaccharides (LPS) from the cell wall of gram-negative bacteria.

"Good bacteria" induce local and systemic immune tolerance via metabolic and molecular molecules. Systemically, this is affected by Treg cells that are induced in the gut-associated lymphoid tissue (GALT) via epigenetic changes and maximally induced by a combination of nutrients such as vitamins A and D and probiotics.[3] Lack of these good bacteria leads to the opposite immunophenotype, which is an excess of inflammatory immune cells such as Th1, Th2, and Th17 cells. This results in predispositions toward inflammatory disorders.[2]

Probiotic (good) bacteria also help to reduce intestinal colonization with pathogens by producing antimicrobial substances, promoting mucosal immunity, and occupying receptor sites. Without this colonization resistance against pathogens, the gut is vulnerable to colonization or overpopulation with harmful inflammation-inducing and mucosa-damaging bacteria.[2]

"Good bacteria" also produce metabolites such as short-chain fatty acids (SCFA) that have beneficial effects throughout the body such as suppressing inflammation, promoting antibody production, and modulating gut hormone release, which impacts lipid and lipoprotein metabolism.[3] The SCFA butyrate has a trophic effect on the gut mucosa, helping to heal the gut and prevent a leaky gut, which is associated with systemic inflammation. Lack of such microbe-derived metabolic support predisposes toward failure to maintain a high-integrity mucosal barrier leading to a leaky gut.[2] A well-known consequence of a leaky gut is increased translocation of intestinal bacteria in the GALT and portal circulation, wherein bacterial DNA and LPS promote hepatic damage and systemic inflammation.[2] In fact, it is now appreciated that there is an intraocular microbiome independent of the ocular surface microbiome. In emerging research, the intraocular environment, which was believed to be sterile, has now been shown to contain intestinal bacterial products that have translocated into the bloodstream and internal organs, including healthy eyes and eyes from diseased animal models.[3, 4] Deng at al. evaluated intraocular samples from over one thousand human eyes and using several different methods of testing demonstrated the presence of intraocular bacteria.[3, 5] Importantly, they excluded the possibility that the microbiome from these low-biomass communities could be contaminated from other reagents.[3, 5] They detected a disease-specific microbial signature for the intraocular environment of individuals with AMD and glaucoma, suggesting that either spontaneous or pathogenic bacterial translocation may be associated with these conditions.[3, 5] Prasad et al. showed the importance of the plasma microbiome and the intraocular microbiome in a rodent model of diabetic retinopathy.[3, 6] Many metabolites produced by gut microbiota have been shown to reach the retina and impact retinal function.[3]

PHOTO CREDIT: Yulia Naumenko/Getty Images

Evidence obtained from human and animal studies provides a unifying paradigm of a vicious cycle:[7]

1. CHANGES IN GUT FLORA →
2. DYSBIOSIS →
3. GUT INFLAMMATION →
4. GUT DYSFUNCTION (INTESTINAL PERMEABILITY) →
5. SYSTEMIC INFLAMMATION →
6. NEUROINFLAMMATION →
7. DISPARATE PATHOPHYSIOLOGICAL ALTERATIONS

Gut-Eye Axis

The presence of a gut microbiota-brain axis has been established in the literature. The gut microbiota-brain axis refers to a bidirectional communication network between gut and brain strongly mediated by the immune system.[10] This network is not only anatomical, but it extends to include endocrine, humoral, metabolic, and immune routes of communication as well. Its composition includes gut microbiota and their metabolic products, enteric nervous system, sympathetic and parasympathetic branches, neural-immune system, neuroendocrine system, and central nervous system.[10] The eye, specifically the retina, is an extension of the brain. Emerging data now support the presence of a gut-eye and gut-retinal axis.

Uveitis, age-related macular degeneration, Sjogren's syndrome, diabetic retinopathy, glaucoma, infectious keratitis, and retinitis pigmentosa have all been linked to gut microbiome abnormalities.[10, 11, 12] The link between gut microbiome changes and ocular diseases can be explained by several mechanisms, including the following: dysbiosis-induced increased intestinal permeability allowing microbes and their metabolites to induce ocular cell inflammation; dysbiosis-induced breakdown of the blood-retinal barrier responsible for increased oxidative stress in the retina; and inflammatory processes associated with age-related gut dysbiosis contributing to premature senescence of retinal cells, which, through releasing pro-inflammatory cytokines and angiogenic factors, leads to neovascularization and disruption of vascular repair.[13, 14, 15]

Microbiome Modulation: A New Therapeutic Target for Ocular Diseases

The term probiotic, according to the World Health Organization, identifies all microorganisms able to bring benefits to the health of the host. Probiotics are live microorganisms, which, when administered in adequate amounts, can confer a health benefit to the host. Research on probiotics is exploding. Per Dr. Jason Hawrelak, head of research at **ProbioticAdvisor.com,** in 2021, there were nearly 5,000 papers published on probiotics. It is important to note that research is strain specific. For example, in a commonly used over-the-counter probiotic, *Lactobacillus rhamnosus GG,* genus is the first name of the bacterium (Lactobacillus), species is the bacteria's second name (rhamnosus), and strain is a more specific classification that distributes members of the same species into subgroup based on one or more properties that these bacteria have that are distinct from other members of the species (GG). Lactobacullus, a genus of lactic acid bacteria, is widely used to enhance the intestinal barrier

PROBIOTIC CLINICAL PEARLS:

1. **Probiotics are best taken with a meal:** Research clearly shows improved bacterial survival when probiotics are taken with a meal (preferably a larger meal such as dinner). Dairy, fiber, or grain-based meals optimize survival through the upper GI tract.[1, 2]
2. **Probiotics can and should be given concurrently with antibiotics:** Research shows that concurrent administration of probiotics with antibiotics not only significantly decreases antibiotic-related side effects, but doing so also attenuates antibiotic-associated damage to the gut microbiota.[3] It is good clinical practice to prescribe over-the-counter Lactobacillus rhamnosus GG, a widely available probiotic and one of the most well-researched strains, concomitantly with oral antibiotics to prevent damage to the gut microbiome from antibiotic use. Studies have shown that this single strain also increases levels of Bifidobacterium in the stool.
3. **Probiotics do not permanently colonize the human gastrointestinal tract:** No exogenously supplied probiotic strain permanently colonizes the human GI tract. Once you stop taking a certain strain, it will eventually die off. You cannot re-colonize permanently by taking probiotic supplements for a limited time.
4. **Two widely available probiotics strains that have been shown to help repair a leaky gut are Lactobacillus rhamnosus GG and Saccharomyces boulardii:** Lactobacillus rhamnosus GG has been extensively studied and has shown positive effects on tight junction function. It enhances the expression of proteins that contribute to tight junction integrity such as zonula occludens-1 and occludin.[4] Saccharomyces boullardii is a beneficial yeast that was once available by prescription only, but it is now widely available over the counter. It has been shown in studies to increase the expression of tight junction proteins and improve barrier function.[5]
5. **Research conducted on one probiotic strain cannot be accurately extrapolated to other strains within the same species:** To assess the quality of a supplement or probiotic food, you need to know not only the species of bacteria but also the strain because different probiotic strains have different actions. For example, one study found strain 299v of species, Lactobacillus plantarum, significantly decreased abdominal pain severity, frequency, and bloating in patients with irritable bowel syndrome (IBS).[6] However another study with the same species but different strain, Lactobacillus plantarum MF 1298, significantly worsened IBS symptoms, so much so that patients preferred the placebo.[7]

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and immune function. *Lactobacillus paracasei* KW3110 is a strain of lactobacillus that has been particularly studied for its eye benefit. This strain has been shown to suppress retinal inflammation by reducing cytokine-producing macrophages and the loss of age-related retinal cells.[10, 16] Likewise, other experiments demonstrated the ability of the *Lactobacillus paracasei* to suppress inflammation on photoreceptor cells in a murine model of light-induced retinopathy. Researchers from Brigham and Women's Hospital in Boston just announced that they have designed a probiotic to suppress autoimmunity in the brain for diseases such as multiple sclerosis (which often presents with optic neuritis). In their study, published in *Nature,* the researchers engineered a probiotic that produces lactate and suppresses T cell autoimmunity through the activation of signaling pathways in dendritic cells (immune cells involved in the regulation of autoimmune responses directed against myelin). After identifying an immunometabolic pathway that regulates dendritic cell function, they developed a synthetic probiotic for its therapeutic activation that was able to suppress inflammation in the brain.[17]

Alongside probiotic biotherapy, there is also the use of prebiotics and postbiotics. Prebiotics are a substrate that is selectively utilized by host microorganisms conferring a health benefit. Fructooligosaccharides (FOS), inulin, and galactooligosaccharides (GOS) are prebiotics that, through fermentation, have been shown to increase the presence of Lactobacilli and Bifidobacteria by producing beneficial metabolites, promoting the absorption of calcium, reducing protein fermentation, reducing pathogen bacteria, counteracting intestinal permeability, and enhancing immune function.[10, 18]

Postbiotics are a mixture of metabolic substrates released by the microorgansims that directly or indirectly may promote health benefits to the host. Examples of postbiotics include the short-chain fatty acids butyric acid (butyrate), acetic acid (acetate), and propionic acid (propionate). These are byproducts of the breakdown of dietary fibers from foods such as fruits and vegetables.

A lot of work still needs to be done to identify specific probiotic strains related to particular diseases, but the future management of many ocular diseases may very well involve probiotic manipulation with specific strains. First and foremost, practitioners must do no harm. Contraindications do exist in the literature for the use of probiotics such as in those who are immunosuppressed or are in the ICU.[19]

The future management of many ocular diseases may very well involve probiotic manipulation with specific strains.

Using Food as Medicine: Dietary Patterns That Support a Healthy Microbiome

Diet is the most powerful influencer of the health of the gut microbiome. First and foremost, a heavily plant-based diet high in vegetables, fruit, and fiber is key to supporting a diverse, healthy inner ecosystem. Many if not most beneficial microorganisms are plant eaters. We need a rainbow of plant foods a day, and the more species we consume, the better for our microbial diversity. We also need to increase fiber. The average American only consumes around 15 grams of dietary fiber a day, which is well below the 25 to 38 grams recommended by the USDA's Dietary Guidelines for Americans. Our ancient ancestors consumed between 100 to 150 grams of fiber per day. Dr. Eric Alm of MIT found that adding just 10 more grams of dietary fiber per day led to 11% more diversity in our microbiota.

Increasing consumption of probiotics and/or fermented foods such as miso, yogurt, kefir, sauerkraut, tempeh, kimchi, and kombucha leads to a healthier microbiome. It is recommended to consume at least one of these per day as this has been shown in studies to significantly decrease systemic markers of inflammation.[8] The gut responds quickly to positive changes in diet as changes in the gut microbiome can be seen in as little as 24 hours after changing food choices.[8]

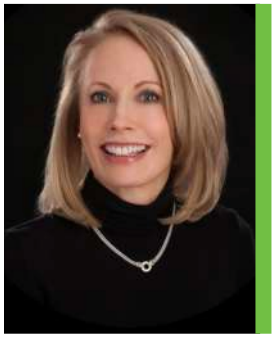
Limiting processed foods and added sugar is important. Processed foods contain emulsifiers and detergent-like compounds that can damage the intestinal lining, leading to a leaky gut and systemic inflammation. Sugar feeds pathogenic bacteria. High sugar diets can be thought of as throwing lighter fluid on the fires of inflammation.

One size does not fit all when it comes to optimal diet, however, overall patterns have emerged in research as the best for promoting health. High animal protein diets, high fat diets, and diets high in refined carbohydrates have been shown to contribute to dysbiosis. The Mediterranean diet, which is

high in green vegetables and fish and lower in simple carbohydrates, plays a role in shifting gut microbial composition, favoring greater diversity and higher levels of beneficial short chain fatty acids, thereby reducing systemic inflammation. Mediterranean diets have been shown to be protective in AMD.[3]

Vitamin A and vitamin D deficiencies result in less diverse microbial populations, and supplementation with vitamin D has been shown to increase fecal levels of SCFA.[3] Relative sufficiency versus deficiency in calcium, magnesium, and zinc can also reshape the microbiota.[3, 8] Vitamins E and C have been shown to promote an anti-inflammatory gut microbiome in humans.[3]

You cannot supplement your way out of an unhealthy diet. Fermented foods, plant-based foods, and fiber are more important than over-the-counter probiotics. However, commercially available, evidence-based probiotic supplements do confer benefit based on individual health challenges and strain-specific, targeted research. It's interesting to note that when *The New York Times* journalist and best-selling author, Michael Pollan, asked the top experts in the field of microbiome research about their use of probiotics, most do not take them but rather focus more on a whole-foods diet rich in fiber and fermented foods.[9] ■



Dr. Julie Poteet, OD, MS, CNS, FOWNS, graduated from The New England College of Optometry and then completed a residency in primary care and ocular disease at the VA Medical System in Boston. At the VA, Dr. Poteet became interested in why some veterans seemed to age so differently from their peers and began questioning what lifestyle factors have the greatest impact on health and vitality. She then went on to complete a Master of Science in Human Nutrition and Functional Medicine. After earning her Master's Degree, she then completed the requirements to become a Certified Nutrition Specialist in 2015, becoming one of the first ODs to attain CNS certification. Dr. Poteet served as Vice President of the Ocular Wellness & Nutrition Society (OWNS) for six years under her mentor Dr. Stuart Richer, and she served as President of OWNS for three years. She has lectured extensively on the microbiome and immune system dysfunction. She works in Atlanta, where her office is a Macular Degeneration Center of Excellence. She is a member of the American Nutrition Association, formerly the American College of Nutrition. Dr. Poteet is passionate about carrying on the legacy of her mentor, Dr. Stuart Richer, whose mantra "repair the roof before it starts raining" is an excellent metaphor for using lifestyle and nutrition to mitigate the course of disease.

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The Profound Impact of Sleep on Ocular Health

BY KALEB ABBOTT, OD, MS, FAAO

In our bustling lives, sleep is often relegated to the bottom of our priority list. Although patients and eye care providers are aware that sleep impacts overall health, few people specifically consider the impact of sleep on eye health. Sleep duration and quality is crucial for the proper functioning and maintenance of our ocular system. This intriguing relationship between sleep and eye health highlights the various ways in which sleep deprivation and poor sleep habits can compromise our vision and ocular health.

The Role of Sleep in Ocular Surface Disease

The eye's surface, like other areas of the body such as the mouth, nostrils, and throat, is covered by a mucous membrane. However, there is a significant difference – the eyes are constantly exposed to the environment during waking hours, with the tear film being their only form of protection. In contrast, other mucous membranes may be located internally (e.g., throat) or only partially exposed with additional protective factors (e.g., nostrils with nasal hair). This continuous exposure to the environment often leads to dryness of the eyes throughout the day. Therefore, sleep plays a crucial role in the healing and recovery of the eyes from the drying effects experienced while awake.

Extensive research indicates a strong association between poor sleep quality and dry eye disease. In fact, dry eye disease is more closely linked to poor sleep quality than even sleep apnea (Magno et al., 2021).[1] Individuals with dry eye disease are 1.5 times more likely to experience poor sleep, while those with poor sleep are 50% more likely to have dry eye disease (Magno et al., 2021).[1] Studies have shown that just one night of sleep deprivation in humans can increase tear osmolarity, reduce tear break-up time, and decrease lacrimal gland secretions (Lee et al., 2014).[2]

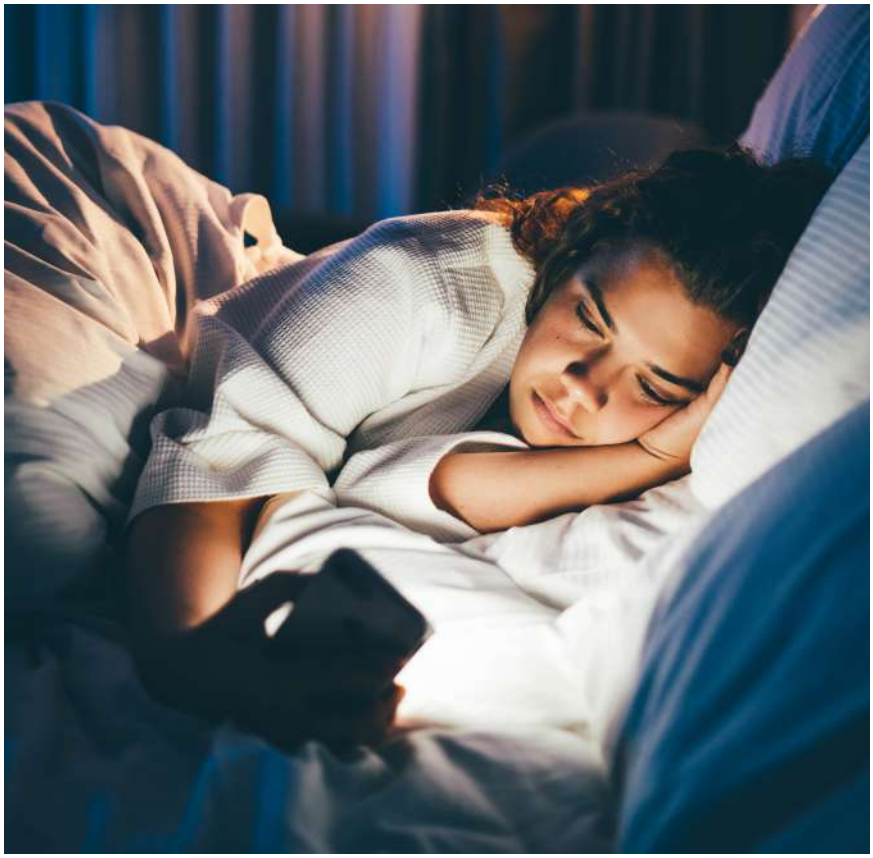
In mice deprived of sleep for two days, there is a 50% decrease in lacrimal gland secretions, increased corneal sensitivity, and increased corneal staining (Li et al., 2018).[3] In my experience, corneal staining caused by sleep deprivation often resembles the diffuse fine punctate staining observed in autoimmune-related ocular surface disease (OSD). This similarity can be attributed to the fact that both conditions can lead to a decrease in lacrimal gland secretions.

Fascinatingly, emerging theories suggest that rapid eye movements during sleep may promote aqueous humor flow, influencing corneal nourishment, and contribute to the spread of the tear film (Modarreszadeh et al., 2014;[4] Murube, 2008).[5] While ongoing research continues to shed light on these mechanisms, it is evident that the benefits of sleep on OSD extend beyond mere physical protection of the eyes. Having said that, the eyelids play a pivotal role in protection of the ocular surface during sleep.

Eye Closure and Sleep

It is not uncommon for the eyelids to remain partially open during sleep, with the extent of the gap varying from a slight incomplete lid seal to more pronounced nocturnal lagophthalmos (Blackie & Korb, 2015).[6] This incomplete lid closure may be exacerbated in conditions such as floppy eyelid syndrome (related to obstructive sleep apnea), eyelid laxity, or post eyelid surgery (ex. blepharoplasty). Individuals with obstructive sleep apnea (OSA) are already at a higher risk of developing OSD due to changes in eyelid anatomy. However, this risk is further increased for those who use a continuous positive airway pressure (CPAP) device, as the directed airflow from the device during sleep may affect the eyes (Shah et al., 2021).[7]

Sleep duration and quality is crucial for the proper functioning and maintenance of our ocular system.



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Sleep Disorders and Eye Disease

OSA is associated with a wide range of conditions, including glaucoma, floppy eyelid syndrome, keratoconus, dry eye disease, non-arteritic anterior ischemic optic neuropathy, retinal vein occlusion, papilledema, diabetic retinopathy, and central serous chorioretinopathy (Lee et al., 2022;[8] Santos & Hofmann, 2017).[9] The ocular manifestations of OSA arise from vascular and mechanical effects of the condition, such as decreased elastin, weakness in connective tissues, promotion of inflammatory cascades, and hypoxic events (Santos & Hofmann, 2017).[9] While all sleep disorders have the potential to harm the eyes, OSA is the most prevalent sleep disorder and the most recognized threat to ocular health (Ram et al., 2010).[10]

However, it is crucial to recognize that OSA is not the only sleep-related condition that influences eye health. Research has indicated that chronic sleep deprivation can increase the risk of developing visually threatening eye conditions such as glaucoma (Groff et al., 2022)[11] and age-related macular degeneration (Sia et al., 2022).[12] Sleep deprivation compromises the eyes' ability to repair and regenerate, heightening susceptibility to these conditions. Given the connection between sleep disorders and cardiovascular disease, it is not surprising that metabolically demanding areas of the eyes are also vulnerable to sleep disorders (Plante, 2006).[13]

We even know that sleep deprivation can lead to physical manifestations in the eyes, such as eyelid myokymia (Kelly IV et al., 2018).[14] This bothersome and persistent eyelid twitching serves as a reminder of the importance of not neglecting sleep. It is crucial to pay attention to these signals our body provides us with.

The Impact of Sleep on Binocular Vision and Refractive Error

In modern society, sleep is often in direct competition with screens and devices. Prolonged periods of screen time, particularly during sleep-deprived nights, can strain the eyes and contribute to symptoms such as eye fatigue, blurred vision, diplopia, and headaches. Collectively, this is known as asthenopia. Both excessive near work and poor sleep habits contribute to asthenopia.

As clinicians, we are well aware of how fatigue affects binocular vision. It is reassuring to find that the literature confirms the impact of poor sleep on binocular vision functions such as convergence (Horne, 1975),[15] saccadic eye movements (Zils et al., 2005),[16] and diplopia (Thomas et al., 2000).[17] In fact, lack of sleep has been implicated in symptoms of asthenopia for centuries (Mackenzie, 1843).[18]

Furthermore, emerging research is identifying links between sleep and refractive error. There appears to be an inverse relationship between sleep and myopia, highlighting the importance of emphasizing proper sleep habits not only in adults but also in children whose refractive errors are still developing (Ayaki et al., 2016;[19] Jee et al., 2016).[20] This association underscores the significance of prioritizing healthy sleep practices for optimal eye health in individuals of all ages.

Circadian Rhythm Photoentrainment

While it is known that sleep disorders or poor sleep habits can jeopardize ocular health, it is also important to recognize that certain eye diseases can predispose patients to sleep dysfunction due to damage to the

intrinsically photosensitive retinal ganglion cells (ipRGCs). The existence of a third photoreceptor (distinct from rods and cones) was first proposed by Clyde Keeler in 1923, when he observed intact pupillary light responses in mice lacking rods and cones (Keeler et al., 1928).[21] In 1999, Russell Foster discovered robust pupillary light responses, melatonin suppression, and light-influenced circadian rhythm cycles in mice devoid of rods and cones (Lucas et al., 1999).[22] Finally, in 2002, David Berson confirmed the existence of a subset of retinal ganglion cells responsive to light, which were dubbed intrinsically photosensitive retinal ganglion cells and are the only photoreceptors located in the inner retina, as opposed to rods and cones in the outer retina (Berson et al., 2002).[23]

While rods and cones project to visual forming brain areas (lateral geniculate nucleus, olivary pretectal nucleus, superior colliculus), ipRGCs project to various brain regions, predominantly non-image-forming areas, including the suprachiasmatic nucleus (SCN), intergeniculate leaflet, hypothalamus, ventrolateral preoptic area, lateral hypothalamus, amygdala, centro-medial nucleus in the thalamus, and lateral habenula (Mure, 2021).[24] The regulation of circadian rhythm primarily occurs through a subset of ipRGC axons that travel to the SCN, which serves as the site of the master circadian clock (Gooley et al., 2003).[25] The primary non-image-forming roles of ipRGCs include circadian rhythm photoentrainment and pupillary light responses (Ksendzovsky et al., 2017).[26] Recent evidence also suggests visual roles of ipRGCs, including their involvement in myopia development (Liu et al., 2022;[27] Lucas et al., 2020).[28]

Understanding that ipRGCs modulate circadian rhythm and regulate sleep-wake cycles, it is important to be mindful that patients with retinal or optic nerve diseases may be more prone to sleep disorders (Czeisler et al., 1995;[29] Wee & Van Gelder, 2004)[30] Such conditions include glaucoma, advanced age-related macular degeneration, retinitis pigmentosa, and diabetic retinopathy (Guo et al., 2017)[31] (Ishibashi et al., 2017;[32] Kardon et al., 2011;[33] Maynard et al., 2017).[34]

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The Importance of Sleep Hygiene

As the connection between sleep and eye health becomes increasingly apparent, it is imperative to discuss with patients that quality sleep is an integral part of overall well-being. The impact of sleep on eye health is multifactorial, affecting tear production, eye muscle function, refractive error, and the risk of developing various ocular conditions. Conversely, eye care professionals should also be aware that certain eye conditions may contribute to sleep dysfunction in patients. By embracing good sleep habits, we can optimize eye health, reduce eye fatigue, and mitigate ocular surface disease. It is important for us to make clear with our patients that a good night's sleep is not only rejuvenating for the body and mind but also a vital investment in the health of our eyes. ■

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Vision in Motion: Unveiling the Eye-Opening Benefits of Exercise

BY KALEB ABBOTT, OD, MS, FAAO

The benefits of exercise on physical and mental health have been recognized for centuries. As early as 450 B.C., Hippocrates stated, "Walking is man's best medicine." He also said, "If there is a deficiency in food and exercise the body will fall sick." While exercise's impact on overall health is well established, its relationship with eye health has gained significant attention only in recent years. By examining the physiological mechanisms involved, we can explore the intricate connections between exercise and eye health, including the impact of exercise on ocular blood flow, retinal health, neuroprotection, ocular surface disease, and the prevention of ocular diseases.

The referenced literature indicates that exercise holds the potential to be a non-invasive and cost-effective method for maintaining and improving visual function. Understanding these connections may pave the way for eye care professionals to better advocate for healthy lifestyle choices, particularly in relation to ocular health.

Exercise, Cardiovascular Health, and Ocular Physiology

The age-old adage that "the eyes are the window to the soul" has persisted for generations. Ocular health and vision are strongly related to the quality of life (Assi et al., 2021) and overall health (Kini & DeLong, 2012). Meanwhile, physical activity has been shown to have an inverse relationship with all-cause mortality (Feng et al., 2023) and is recommended for improving overall health and preventing a wide range of systemic diseases (Garber et al., 2011).

Even small amounts of weight loss and moderate physical activity have been found to reduce the incidence of type 2 diabetes mellitus by over 50% (Dunkley et al., 2014; Knowler et al., 2002). Similarly, the incidence of hypertension and cardiovascular disease is inversely proportional to physical activity (Rossi et al., 2012). Even in the elderly, exercise training may restore coronary microvascular endothelial function (Hotta et al., 2017).

Research has shown that ocular health and cardiovascular health are closely intertwined (Chan et al., 2023). The benefits of exercise on cardiovascular health are far-reaching and include augmented blood circulation, decreased inflammation, higher insulin sensitivity, weight management, enhanced endothelial function of blood vessels, reduced triglyceride levels, increased HDL cholesterol, lower blood pressure, better oxygen utilization, stress reduction, and improved sleep metrics

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(Fiuza-Luces et al., 2018; Nystoriak & Bhatnagar, 2018).

Fascinatingly, studies have demonstrated the ability to use retinal blood vessel imaging as a means to predict an individual's risk of cardiovascular events such as stroke, coronary heart disease, hypertension, diabetes, dyslipidemia, and obesity (Streese et al., 2020). The link between retinal health and cardiovascular health is so strong that retinal blood vessel analysis is now being used to predict overall cardiovascular risk and outcomes.

Given the established connection between cardiovascular health and ocular health, it is unsurprising that exercise would be of tremendous value to ocular health. The retina is one of the most metabolically active tissues in the body and, therefore, highly susceptible to cardiovascular insult. It makes sense then that improvement of blood vessel function in the retina may decrease the risk of retinal disease.

Exercise Can Improve Ocular Blood Flow

Literature on physical exercise often classifies types of exercise as either dynamic or isometric, depending on the mechanical action of the muscles involved. Dynamic exercise involves a change in skeletal muscle length, joint movement with rhythmic contractions, and a relatively small intramuscular force (e.g., jogging and cycling), while isometric exercise is performed in more static positions with a relatively large intramuscular force (e.g., weight lifting).

Studies have demonstrated the ability to use retinal blood vessel imaging as a means to predict an individual's risk of cardiovascular events.

Both isometric and dynamic exercise have been proven to improve blood flow in ocular tissues (Okuno et al., 2006). Such exercise can enhance ocular perfusion pressure (OPP) and blood flow to the retina and choroid (Okuno et al., 2006). Improvement in OPP is especially important in glaucoma, as low perfusion pressure of the optic nerve is a risk factor for both glaucoma development and progression (Leske et al., 2007). OPP is an important metric in glaucoma and is defined as mean arterial blood pressure (BP) minus intraocular pressure (IOP), with mean arterial BP defined as 2/3 [diastolic BP + 1/3 (systolic BP – diastolic BP)]. In layman's terms, it is the pressure at which blood enters the eye. Some studies have indicated that OPP is a more powerful risk factor for glaucoma progression than IOP (Leske et al., 1995). OPP signifies how BP and systemic cardiovascular health relate to glaucoma progression and may offer one explanation as to why exercise mitigates the risk of glaucoma formation and progression (Zhu et al., 2018). While physical exercise is known to improve OPP, it appears that the effect may be somewhat dampened through the autoregulation mechanism, which is the eye's attempt to maintain constant blood flow despite changes in OPP. More research is needed to understand the complex relationship between exercise, OPP, and autoregulation.

Physical activity is known to have profoundly beneficial effects on both small and large vessel disease. The retina's intricate vasculature and high metabolic demand make it susceptible to microvascular insults such as strokes, clots, and ischemia. Both short-term and long-term exercise routines have been shown to enhance retinal microvascular health in both children and adults (Streese et al., 2020). Evidence of these benefits can be observed through fundus photography, which shows changes in central retinal arteriolar and venular vessel diameters. Widening of these vessels may counteract small arterial disease and unhealthy microvascular remodeling over the course of a lifespan. Refinement of retinal blood vessel architecture leads to increased blood flow, oxygen availability, and nutritional support to the retina. Conversely, evidence also demonstrates that a sedentary lifestyle and obesity are associated with small retinal blood vessel diameters (Sousa-Sá et al., 2020). Another mechanism through which exercise is protective against retinal damage is through ameliorated expression of heat shock proteins, which are known to alleviate the harmful effects of oxidative stress and reactive oxygen species (Szyller & Bil-Lula, 2021).

Both human and animal models have demonstrated that in subjects with diabetic retinopathy, running on a treadmill five days per week for 30 minutes per day lessens diabetes-induced apoptosis in retinal cells (Kim et al., 2013). Mouse models have also shown a protective effect of exercise on photoreceptor function and death in retinal degenerative conditions (Lawson et al., 2014). Even voluntary running by mice with inherited retinal degenerations

shows a higher degree of preserved retinal function compared to mice who are unable to exercise (Hanif et al., 2015). Furthermore, exercise helps prevent the conversion of macular degeneration from dry (atrophic) to wet (exudative) (Munch et al., 2013). Conversely, abdominal obesity increases the risk of macular degeneration progression (Seddon et al., 2003). As illustrated, the effects of exercise on retinal health are robust and far reaching.

Modify Intraocular Pressure with Exercise

Glaucoma stands as one of the leading causes of irreversible vision loss worldwide, responsible for 12.3% of blindness (Zhu et al., 2018). While many forms of glaucoma are not directly caused by elevated IOP, IOP reduction remains a well-known modifiable risk factor and the primary treatment method for delaying disease progression. By reducing IOP, we can alleviate mechanical pressure on the optic nerve fiber bundles, thereby improving axonal transportation of nutrients and enhancing OPP.

Decades of research have shown that regular and consistent aerobic exercise can effectively reduce IOP in glaucoma patients not only in the short term but also over the long term (Passo et al., 1992; Passo et al., 1991). This reduction in IOP may lead to a decreased risk of primary open-angle glaucoma progression (Tsai, 2008). While we have some knowledge about the short-term effects of various exercise forms such as walking, running, yoga, cycling, swimming, and weight lifting, further research is needed to understand the long-term effects of these specific exercise routines on IOP reduction (Zhu et al., 2018). Nevertheless, it is clear that aerobic exercise provides long-term benefits for managing IOP in glaucoma.

Neuroprotective Effects of Exercise

Exercise offers tremendous benefits for myriad neurological conditions, particularly in countering the onset and progression of neurodegenerative disorders (Liu et al., 2023). Although the eye is often considered a separate organ system, there is significant overlap between ocular and neurological health through the retinal ganglion cell (RGC) layer and the optic nerve. In fact, some arguments suggest that glaucoma is essentially an ocular manifestation of neurodegeneration and is closely linked with other neurodegenerative conditions such as Parkinson's and Alzheimer's (Ramirez et al., 2017).

The protective role of exercise in neurodegenerative disease is well established, partially attributed to the exercise-induced production of neurotrophic factors, which are known to be downregulated in neurodegenerative disorders. This highlights the fundamental importance of neurotrophic factors in maintaining brain health. Physical activity enhances the release of brain-derived neurotrophic factor (BDNF), nerve growth factor, insulin-like growth factor (IGF-1), glial cell line-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4. These factors promote neurogenesis, neuroplasticity, neuronal survival, angiogenesis, myelination, synaptic plasticity, neuromuscular protection, vascular function, and a neuroprotective role against β-amyloid neurotoxicity (Bonanni et al., 2022).

In particular, exercise-induced release of BDNF and IGF-1 has demonstrated remarkable benefits within the visual pathways, preventing RGC loss and preserving retinal function in cases of optic nerve and retinal disease (Chrysostomou et al., 2016; Zhu et al., 2018) (Rajala et al., 2022). Physical activity also improves neuronal plasticity in neurodegenerative disorders (El Ali et al., 2014). Aerobic exercise has been shown to delay RGC death after injury to the optic nerve (He et al., 2020). Studies have shown

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that aerobic exercise can delay RGC death after injury to the optic nerve, which is noteworthy as glaucoma is characterized by RGC apoptosis. Therefore, exercise may effectively prevent vision loss related to glaucoma-induced RGC death.

Another potential mechanism for the neuroprotective effects of exercise is enhanced mitochondrial function, which is known to be impaired in neurological conditions such as Parkinson's, Alzheimer's, and glaucoma. In the context of glaucoma, RGCs are particularly vulnerable to mitochondrial dysfunction due to their high mitochondrial density and long axons. Evidence suggests that exercise can reverse mitochondrial dysfunction, reduce reactive oxygen species related to mitochondrial damage, and enhance mitochondrial physiology (Zhu et al., 2018). Therefore, exercise-induced mitochondrial rehabilitation may help halt RGC damage related to glaucoma.

Combat Ocular Surface Disease with Physical Activity

Ocular surface disease is strongly related to overall systemic health and has been linked to countless systemic diseases (Kawashima, 2018) (Kawashima et al., 2020). Therefore, it is not surprising that modifiable lifestyle choices that benefit overall health may also have a positive impact on ocular surface disease.

Studies have shown that exercise programs of only three days per week for 10 weeks can significantly improve self-reported dry eye symptoms (Sano et al., 2018). The improvements in ocular surface disease with physical activity are attributed to various factors, including increases in tear volume, improved tear film stability, reduced inflammatory markers, and decreased oxidative stress (Navarro-Lopez et al., 2023). While most of the literature indicating that dry eye may be improved through exercise focuses on aerobic exercise, one study has revealed that yoga may be effective in improving visual comfort, potentially due to the time devoted to physical activity rather than screen time (Telles et al., 2006).

In addition to improved tear film metrics, another potential explanation for the positive effect of physical exercise on ocular surface disease is the psychosomatic effect of endorphin release by the brain during exercise. This endorphin release has a powerful analgesic effect (Santos & Galdino, 2018) that may reduce ocular pain.

Active Lifestyle Affects Cataracts, Vision, Refractive Error

Cataracts are often considered by eye care practitioners as an indicator of overall health, with unhealthy individuals being more susceptible to early cataract development. Evidence shows that a lower body mass index, greater physical activity, and better cardiovascular fitness are associated with a reduced risk of cataract formation (Williams, 2009). Development of cataracts is linked with high blood sugar and obesity (Ang & Afshari, 2021). We even know that routine walking or running has been shown to delay cataract development (Williams, 2013), while lack of physical activity is associated with an increased risk of cataract formation (Zheng Selin et al., 2015).

The effects of a healthy lifestyle extend to ocular health, with research on exercise and eye health revealing that lower levels of physical activity have been independently associated with worse visual acuity (Swanson et al., 2012). Exercise has even been linked to reduced axial length and myopia risk (Read & Collins, 2011), while sedentary lifestyles in children have been associated with larger refractive errors (Quigley et al., 2019).

Mental Health, Exercise, and Chronic Disease

The role of exercise as a therapeutic intervention for chronic systemic conditions is well established and indisputable (Pedersen & Saltin, 2015). However, these conditions also encompass mental health disorders such as anxiety and depression (Anderson & Shivakumar, 2013), which frequently coexist with various ocular diseases, especially conditions associated with vision loss and dry eye disease (Purola et al., 2021) (He et al., 2022). As a result, utilizing exercise as a form of medicine for ocular disease goes beyond improving ocular health; it also holds the potential to enhance the mental well-being of patients grappling with these chronic ailments. Thus, in addition to preventing vision loss and improving ocular comfort, exercise may prove beneficial in promoting overall well-being and elevating the quality of life for patients.

While we commonly recognize the benefits of exercise on our physical and mental well-being, its positive impact on eye health should not be underestimated. Regular physical activity influences ocular blood flow, augments antioxidant defenses, enhances oxygen supply, activates neurotrophic pathways, and improves overall vascular health. These effects may reduce the incidence and progression of conditions such as macular degeneration and glaucoma.

Embracing an active lifestyle offers a promising approach for maintaining healthy eyes.

Furthermore, exercise also has proven positive effects on ocular surface disease and cataracts. The extent of exercise's benefits on ocular health is likely more extensive and robust than currently understood. Further research is necessary to determine the optimal exercise modalities, duration, and intensity for promoting eye health. Nonetheless, embracing an active lifestyle offers a promising approach for maintaining healthy eyes and improving overall quality of life. ■

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One Solution in the Battle Against Dry Eye: Nutrition

BY JEFFREY ANSHEL, OD, FAAO

Dry eye disease has become not only a significant quality-of-life issue but has shown itself to be a very real disease process. Whether it's called dysfunctional tear syndrome, chronic dry eye, or dry eye syndrome, it's a condition whereby the anterior surface of the eye is not properly maintained and/or the patient is experiencing ocular discomfort.

For many years, the logical "treatment" for this condition has been to attempt to supplement the tear film with additional lubrication. The science of lubrication has come a long way, and now we realize that it will require more than just "adding moisture" to resolve this problem. New methods of treatment include enhanced artificial tears, punctal plugs, lipid layer and tear quality enhancements, and epithelial surface treatments. In the past few years, a new approach to resolving this condition has included oral nutritional supplementation. Here are the facts and fiction surrounding the oral treatment of dry eye disease.

Good Fats for Eye Health

Essential fatty acids (EFAs) are involved in producing energy in our bodies from food substances and moving that energy through our systems. They govern growth, vitality, and mental state. They coordinate oxygen transfer, hemoglobin production, and control of nutrients through cell membranes. EFAs play a part in almost every function of our body. Humans do not produce essential fatty acids, so we must get them from our diet. Here are the details on two EFAs, omega-6 and omega-3.

Strike a Balance

Omega-6 fatty acids are the most plentiful in our American diet. They are in most everything we eat that contains fat, including meat, most vegetable oils, dairy products, and eggs. Omega-3 fatty acids are available in many seed oils and almost all cold-water fish. A proper balance of these fatty acids is essential to good health. The Institute of Medicine recommends a daily intake ratio of 4:1[1] — four times as many omega-6 fatty acids as omega-3. It's currently estimated that the average American diet maintains a ratio of 25:1! This pushes the pro-inflammatory action of the omega-6 fatty acids. It has been confirmed that inflammation is a causative factor in the development of dry eyes.

In the past few years, a new approach to resolving this condition has included oral nutritional supplementation.

From Fat to Prostaglandins

Fatty acids are stored in every cell membrane of our body. They have two primary functions. First, they ensure cellular fluidity, acting as sentinel gatekeepers for every cell. They allow vital nutrients to enter the cell and force destructive free radical debris out. Second, nutrient co-factors such as vitamin C, vitamin B6, zinc, and magnesium help our bodies produce enzymes that convert dietary omega-6 and omega-3 fatty acids into three types of prostaglandins: PGE1, PGE2, and PGE3.

- **PGE1 prostaglandins** reduce inflammation and inhibit blood clotting. They are also capable of reducing pain, swelling, and redness associated with inflammation, particularly in mucosal tissues, including the eyes. Only omega-6 fatty acids can produce this particular type of prostaglandin.
- **PGE2 prostaglandins** can also only be produced by omega-6 fatty acids. These pro-inflammatory prostaglandins constrict blood vessels, increase body temperature, and encourage blood clotting. These events are lifesaving when the body suffers a wound or injury. Without PGE2s, a person could bleed to death from the slightest of cuts, or succumb to a viral or bacterial attack. However, in excess, this type of prostaglandin is harmful because it sets up a chronic inflammatory condition in the body.
- **PGE3 prostaglandins** are available from omega-3 fatty acids. Omega-3 fatty acids, particularly docosahexaenoic acid (DHA),

keep brain cells healthy as well as keeping the rods and cones supple and working properly. The omega-3 fatty acid, eicosapentaenoic acid (EPA), also plays an important anti-inflammatory role. When necessary, it blocks the release of omega-6 arachidonic acid, which will produce pro-inflammatory PGE2.

Without sufficient omega-3s in the diet, chronic inflammation can become a problem, one that is now linked to many degenerative diseases of the eye, including macular degeneration, glaucoma, and diabetic retinopathy, as well as dry eye. As with all dietary intake, a proper balance of EFAs is the key to good health. Most scientists agree that a diet including cold-water fish two or three times a week, or long-chain fatty acid (EPA and DHA) supplementation, helps maintain the proper balance of EFAs.[1]

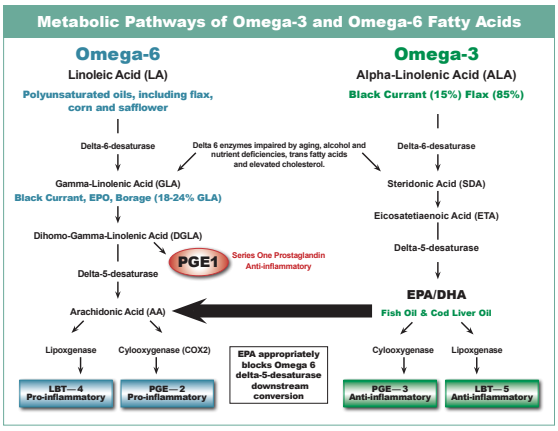

Figure 1. Metabolic Pathway of Essential Fatty Acids

Inflammation

Researchers suggest that omega-6 fatty acids metabolize to the site-specific anti-inflammatory eicosanoid, PGE1. Literature suggests these particular prostaglandins reduce ocular surface inflammation as well as the inflammatory process associated with meibomitis and reduced lacrimal gland aqueous output.[3]

Omega-6 fatty acid has been given a bad rap. It's true that the typical American diet is overloaded with omega-6 linoleic acid (LA) from vegetable oils such as sunflower, safflower, corn, and soybean oils, which are added to nearly all processed foods. Many pantries are far too full of processed crackers, chips, cookies, and cakes — and thus the omega-6 oils that oxidize too quickly to become pro-inflammatory markers. (Figure 1).

However, good health also depends on moderate levels of omega-6 gamma linolenic acid (GLA), which is a downstream metabolite of omega-6 linoleic acid. It's found in sources such a black currant seed oil (preferred), borage oil, and evening primrose oil. This compound is necessary to metabolize omega-6 fatty acid to the series one anti-inflammatory PGE1s, which are associated with healthy mucosal tissue and tear film. The human body cannot metabolize omega-3 fatty acids to these specific anti-inflammatory prostaglandins.

Metabolization Is the Key

Most omega-6 fatty acids are consumed in (polyunsaturated) vegetable oils as LA. Excessive intake of LA is unhealthy, because it can promote inflammation if not properly metabolized. In contrast, omega-6 fatty acids that are successfully metabolized or those that have GLA, reduce inflammation after further metabolizing to dihomo-gamma-linolenic acid (DGLA), which also blocks the pro-inflammatory arachidonic acid conversion. (Figure 1)

Sources of EFAs

Flaxseed oil does not include any GLA, so the body's ability to utilize flaxseed is totally dependent on the unpredictable delta-6 enzymatic conversion of its LA to GLA. As a short-chain omega-3 fatty acid, flax does not contain EPA/DHA. Therefore, it is totally dependent on the conversion of alpha-linolenic-acid (ALA) to EPA/DHA, which is required to produce PGE3. All fatty acids compete for the same metabolic desaturase, so for good health, we should consume fewer omega-6s and more GLA as omega-6s and DHA/EPA Omega-3s.

Put Supplements to Work

A good nutritional supplement should address many of the underlying inflammatory processes associated with dry eye disease. Studies suggest oral administration of specific omega-6 EFAs that contain sufficient amounts of GLA stimulate the natural production of PGE1.[3]

- **Flaxseed oil** is the most unstable of the EFA oils, and it does not contain GLA. Flax stability issues keep it from easily converting to GLA, which it must do to produce PGE1.[4]
- **Pharmaceutical-grade cold-water fish oil**, as a source of omega-3 EPA/DHA, is germane to a good formulation. It serves as a metabolic gateway boost to the downstream conversion of the omega-3 to the anti-inflammatory PGE3. Peer reviewed literature suggests vitamin E, specifically

gamma tocopherols, stabilizes EFAs and prevents oxidation.[5]

- **Experts suggest curcumin** to appropriately block omega-6 and omega-3 fatty acids from metabolizing to the pro-inflammatory PGE2 and IL-1.[6] Curcumin is a natural COX2 inhibitor with chemical properties similar to ibuprofens (NSAIDS), but curcumin does not inhibit production of the COX1 enzyme that's necessary to protect the stomach lining.
- **Vitamin C,** as ascorbic acid and fat-soluble absorbyl palmitate best modulates PGE1 synthesis due to the extended half-life of the fat-soluble vitamin C over water-soluble ascorbic acid. This vitamin C combination also enhances the production of immunoglobulin E concentrates in tears, the first line of basophil and mast cell defense against invading pathogens that can cause dry eye symptoms.
- **Studies also recommend lactoferrin** to increase the level of iron-binding proteins to better inhibit viral and bacterial infections and to balance other tear proteins, which modulate the surface tension of the tear film.[7-9] Lactoferrin is a mucous-specific anti-inflammatory agent. Neutrophils, the first line of defense against infection, are located in the tear film and produce lactoferrin. Neutrophil apoptosis signals the macrophage to clean up debris from wound sites, including surgically induced wounds (think LASIK).

Find the Lucky Combination

Treating idiopathic dysfunctional tear film with oral nutritional supplements can be an effective method to resolve this frustrating and uncomfortable condition. While it's worthwhile to uncover the cause of the condition, using the right combination of ingredients can work regardless of the causative factors.

Patient Education

Educating patients is a challenging task because many may not be aware of their nutritional balance. While a qualified nutritionist should make complete recommendations of nutritional supplements, eye care providers can offer them valuable information about treating chronic eye disease. Review the various companies that supply eye-related nutritional products, and look at their rationale for their products. Be sure the ingredients are backed by qualified research studies. Most doctors are making a "recommendation" for a nutritional supplement, rather than "prescribing" it, but the patients will value the doctor's opinion as an eye care expert.

Success!

When a patient presents with a likely dry eye condition, briefly discuss the anatomy of the tear layer and explain why they are experiencing their symptoms. Then discuss the recommended product and the rationale for doing so. Offer them a brochure from the manufacturer and let them consider the process. Suggest a timeline where they may notice a difference in their condition. This is good for the practice, for the patient, and for the bottom line! ■

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Age-Related Macular Dysfunction: A Multifactorial Approach

BY KERRY GELB, OD

Age-related macular degeneration (AMD) is the leading cause of legal blindness in the U.S. Studies show AMD is more prevalent than glaucoma and diabetic retinopathy combined. Three of the most common disease conditions seen in an optometric physician's office, dry eye, diabetes, and AMD are caused in part by nutrition and lifestyle. According to Donoso et al.,[1] AMD should be considered a systemic vascular disease and is more common in people with other chronic disease states, cardiovascular disease, hypertension, obesity, diabetes, and other diseases of inflammation. The question is: Why do these disease states run together, and did these diseases even exist before the 1900s?

According to the National Institutes of Health (NIH), AMD affects one in three people over the age of 75, but according to Chris A. Knobbe and Suzanne J. Alexander in their book *The Ancestral Diet Revolution,* there were fewer than 50 reported cases of AMD before 1851.[2] They also point out that heart attacks, stroke, cancer, Alzheimer's, osteoarthritis, diabetes, metabolic syndrome, and obesity were also extremely rare or nonexistent before the 1900s. So what has changed?

What Has Changed in the Last Century?

When we explore changes over the last 100 years, we need to look at the American diet, exercise, chronic stress, sleep, and medications. According to the United States Department of Agriculture, 63% of the foods Americans consume are processed, approximately consisting of refined sugar 21%, refined wheat 17%, trans-fat 1%, seed oils 33%. Real whole food only consists of 29% of the American diet. Obesity has been on a steady increase, especially since the 1960s. According to the CDC, the average weight of a U.S. female is now 166 pounds, about the same weight as the average man in the 1960s, while the average man now weighs just under 200lbs.

'Inflammaging'

Inflammation is considered the core component of chronic disease. Underlying factors of inflammation include a new concept called "inflammaging." According to the NIH, inflammaging is defined as an age-related increase in the levels of pro-inflammatory markers in blood and tissues, and it is a strong risk factor for multiple diseases that are highly prevalent and frequent causes of disability. Inflammaging carries high susceptibility to chronic morbidity, disability, frailty, and premature death (Ferrucci et al., 2018).[3]

According to Mark Hyman, MD, lifestyle choices that cause inflammation can lead to chronic morbidity, disability, frailty, and premature death. Poor nutritional density, lack of phytochemicals in foods, inadequate sleep, environmental toxins, lack of exercise, toxic relationships, negative thoughts, and chronic stress are all lifestyle factors that lead to inflammation. Hyman[4] points out that comorbidities are diseases that often run together. They include hypertension, type 2 diabetes, cardiovascular disease, kidney disease, and as stated earlier by Donoso, AMD. Hyman points out they are not "co anything and that these chronic disease states are all caused by the same thing." He states that we're currently treating these comorbidities separately with different medications by multiple specialists. Hyman's functional medicine approach is the manner in which modern doctors should address how these comorbidities are connected, taking a unified approach to addressing root causes of disease and restoring health, optimizing and regenerating function.

Hyman uses cardiovascular disease as an example by stating, "90% of CVD can be preventable by lifestyle changes and reversing the following: eating refined foods full of sugar, starch, processed fat, and refined oils, (salt, sugar, and oils are added by food companies to make processed foods more palatable), sitting for hours, chronic stress, loneliness, lack of family units, exposure to pollution, heavy metals, and pesticide exposure, all causing chronic inflammation and eventually leading to chronic disease based on epigenetics." Epigenetics is the study of how one's behaviors and environmental exposures can cause changes that affect your health and gene expression. The good news is epigenetic changes are reversible. According to a study by Gray,[5] 80% of chronic disease is due to poor lifestyle, diet, and environmental exposure, and only 20% is pure genetics.

The Cause of Age-Related Macular Degeneration

All disease is a combination of genes and environment. Conventional teaching states AMD is a multifactorial disease with genetics responsible for 45-70% of the etiology. *The Ancestral Diet Revolution* explains how this is not possible since human genetics hasn't changed over the past 100 years, but the incidence of AMD has exploded to epidemic proportions. So, what has caused the epidemic rise in AMD if it's not genetics because human genetics hasn't changed? Knobbe theorizes that displacing evolutionary foods with processed foods is the primary and proximate cause of AMD, and he makes the case that seed oils are the major culprit.[6] In *The Ancestral Diet Revolution,* he shows numerous correlation studies that the increase in human consumption of seed oils is not only the main trigger for AMD but the primary trigger for many other chronic disease as previously outlined.

"Displacing evolutionary foods with processed foods is the primary and proximate cause of AMD." - Knobbe

Tan's 2020 paper[7] explains, "Local inflammation leads to drusogenesis, RPE/photoreceptor degeneration, Bruchs membrane disruption and the development of CNV." It is interesting to note that the RPE releases many inflammatory mediators, causing chronic destructive inflammation. When homeostasis is lost, according to Tan, between pro-inflammatory and anti-inflammatory responses, AMD occurs. Simply, inflammation plays an essential role in the pathogenesis of both dry and wet AMD.

How to Reduce the Risk of AMD

With this knowledge, what can we do to help patients decrease the risk of AMD? Most importantly we want to decrease chronic inflammation and reverse the well-known risk factors. Preventive or remedial efforts include:

1. Stop smoking: The biggest modifiable risk factor for AMD is smoking. Current smokers carry a 2.5 to 4.8 times higher risk than non-smokers for developing AMD.

2. Control lipids: Increasing levels of high-density lipoprotein (HDL) cholesterol was inversely related to incident late AMD. Elevated total/HDL cholesterol ratio predicted late AMD.

3. Reverse obesity: Higher body fat percentage, even within relatively healthy limits, is associated with lower tissue lutein and zeaxanthin status. The results indicate that adiposity may affect the nutritional state of the retina (Hammond).[8] A 32% increase in the risk of developing late AMD was noted among obese individuals. In fact, BMI shows a linear dose-response relation with AMD risk. Educate your patients that a reduction in the waist-to-hip ratio can decrease the risk of AMD.

4. Exercise: Physical activity decreases the risk of AMD. A Mares et al. 2010 study showed a healthy diet, not smoking, and physical activity lower the risk for AMD by 71%.[9] A study in *Investigative Ophthalmology & Visual Science* demonstrated certain running routines decreased cataracts and AMD.

5. Decrease processed sugars: High glycemic diets showed a 49% increased risk of AMD (Allen Taylor PHD Tufts.)[10]

6. Stop drinking: Heavy alcohol consumption was significantly associated with an elevated risk of early AMD. Alcohol depletes antioxidants (zinc, thiamine, vitamin A) and increases oxidative stress. (AJO 2010,2007, Am J Epid BDES).[11, 12] The importance of safe zinc intake for decreasing the risk of AMD levels was demonstrated in the AREDS 1 and 2 studies.

The Holy Grail of AMD prevention has centered around macular pigment. Bone and Landrum[13] identified that macular pigment, also known as carotenoids, is made

from meso-zeaxanthin, zeaxanthin, and lutein. Macular pigment protects the RPE, choriocapillaris and the photoreceptors. Macular pigment protects the macula by filtering and preventing blue light damage, housing antioxidants as a protection against high-risk oxidative stress, quenching singlet oxygen that scavenge free radicals, and protecting against chronic inflammation in the macular region.

Numerous food and supplement studies have shown people with diets high in macular carotenoids lower their risk for AMD progression and prevention. Nolan et al. in 2006 and 2007 published that healthy subjects without evidence of AMD who are at risk of the disease show a relative lack of MP years before onset of clinical disease?"[7] Numerous studies confirm that low macular pigment optical density is associated with an increased risk of developing AMD (Ramen).[14]

Seddon[15] et al., in the landmark 1994 *JAMA* study, showed subjects whose food consumption contained the highest lutein and zeaxanthin content compared to the lowest, decreased the risk of AMD by 43% and that there was linear reduction in risk for AMD.[8]

They also demonstrated foods highest in lutein and zeaxanthin showed a decrease in cataract formation. Amazingly the study showed that lutein and zeaxanthin in the highest quantile group protected past and present smokers against AMD. A 2019 study published in *Ophthalmology* showed the Mediterranean diet significantly reduced risk (by 41%) of developing incident advanced AMD.

Two separate lutein and zeaxanthin plasma studies by Gale and Delcourt[16] revealed the importance of nutrient bioavailability and demonstrated between 50-93% reduction of AMD depending on lutein and/or zeaxanthin plasma content. AREDS study report #22 showed participants reporting the highest intake of dietary zeaxanthin and lutein were less likely to have advanced AMD or intermediate drusen.

Patients with high plasma levels of zeaxanthin had a 93% reduction of AMD. Gale et. al. (*Ophthalmology and Visual Science:* 2003). Low levels of plasma zeaxanthin correlated with significantly higher risk of AMD.

The Blue Mountains Eye Study[17] revealed higher dietary lutein and zeaxanthin intake reduced the risk of neovascular AMD by 65% and confirmed the protective influence of zinc.

Nolan[18] showed macular pigment relates positively to many measures of visual function in "un-supplemented" subjects with early AMD. At six months, lutein, meso-zeaxanthin, and zeaxhanthin improve contrast sensitivity and visual function in patients with AMD.

Most studies have demonstrated a decreased risk of AMD with omega-3 intake in direct contrast to AREDS-2, which showed no benefit.

A meta-analysis (Chong)[18] of nine studies provided data on a total sample size of 88,974 people, including 3,203 AMD cases. A high dietary intake of omega-3 fatty acids was associated with a 38% reduction in the risk of late AMD. In addition, high omega-3 fish intake at least twice a week was associated with a reduced risk of both early and late AMD.

Vitamin D studies have indicated a lower risk of AMD. In one study, Parekh[19] showed those with the highest levels of serum vitamin D had a 40% lower risk of early AMD than those with the lowest levels of vitamin D. This study provides evidence that vitamin D may protect against AMD due to its anti-inflammatory properties.

AMD is a multifactorial disease mostly affected by poor nutrition, lifestyle, and epigenetics. Using an anti-inflammatory lifestyle approach and the proper nutrients can help reduce the risk of the number one cause of elderly blindness in the U.S. ■

Note: AREDS 1 and 2 were not discussed in depth because of the audience familiarity.

Dr. Kerry Gelb, OD, spent three years traveling the continent and Europe producing a feature-length documentary entitled Open Your Eyes, released in 2020. Upon its release, he launched the "Open Your Eyes Podcast" that delivers weekly episodes focusing on all aspects of health. In 2022, "Open Your Eyes Radio" debuted on Salem Radio in Minneapolis and can be heard every Saturday at 10am on 1280 The Patriot. He has also been interviewed for radio and television on topics related to ocular health. He frequently lectures on the diagnosis and treatment of macular degeneration, glaucoma, and diabetes. He has extensive knowledge and expertise in the evaluation and fitting in specialty or "hard-to-fit" contact lenses. He is also certified in the evaluation and management of corneal refractive therapy contact lenses. Dr. Gelb graduated with honors in 1984 from the Illinois College of Optometry, and he completed a one-year residency in the diagnosis and management of ocular disease. Dr. Gelb has been practicing optometry in Woodbridge, N.J., for the past 23 years. He is also a member of the New Jersey Society of Optometric Physicians and the President of ALLDocs (the Association of LensCrafters Leaseholding Doctors).

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10 Foods to Help Prevent AMD

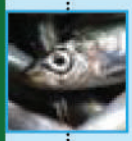
Which foods are the healthiest for your eyes? What can you eat to help fight age-related macular degeneration (AMD), the leading cause of vision loss in the United States in patients over age 50? Here are the top 10 recommended foods that can help support your vision:

1 **Pastured Eggs:** An excellent source of vitamins A, B12 and omega-3. They also contain lutein, zeaxanthin and the amino acid cysteine which all may reduce the risk of cataracts and AMD.

2 **Leafy green vegetables:** Brimming with vitamin C, calcium, beta-carotene and the carotenoids lutein and zeaxanthin. Studies have shown that eating foods rich in lutein and zeaxanthin like spinach, kale and collard greens, can increase the pigment density in the macula and lower the risk of AMD.

3 **Garlic:** Rich in sulfur, garlic is a natural lens protector that's loaded with important antioxidants.

4 **Green vegetables:** Broccoli, bell peppers and Brussels sprouts all help provide a blast of vitamin C, a key antioxidant shown to help protect the eyes.

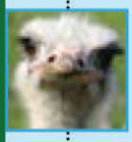


5 **Wild salmon, sardines, anchovies and mackerel:** Certain fish are loaded with omega-3 fats which can help protect the tiny blood vessels in the eyes.

6 **Carrots:** Carrots are loaded with beta-carotene, an antioxidant that helps reduce the risk of cataracts and AMD. Your body converts beta-carotene to vitamin A, which is used by the eye's rods and cones to help the eye perceive light and color.

7 **Goji berries:** Raw goji berries are a great source of antioxidants and contain vitamin C, vitamin E and fiber. Goji berries are also a great source of the carotenoid zeaxanthin.

8 **Orange peppers:** Contain the carotenoid zeaxanthin, which can increase the pigment density in the macula and lower risk of AMD. They have more vitamin C than all other colored peppers, three times the amount of vitamin C as an orange, and the highest vegetable source of vitamin E.



9 **Ostrich and turkey:** Loaded with zinc—one of the key ingredients for maintaining healthy eyes. Turkey also provides the B-vitamin niacin, which helps protect against cataracts.

10 **Sweet potatoes:** Beta-carotene to the rescue once again, thanks to the sweet potato's bright-orange flesh. In fact, sweet potatoes contain some of the highest amounts of beta-carotene of all the vegetables.

10 Ways to Help Prevent AMD

Ask your doctor about age-related macular degeneration (AMD)—the leading cause of severe vision loss for people over the age of 50. AMD has caused vision loss in over 2.7 million Americans and is on the rise.

1 Avoid:

- Smoking
- Weight gain
- High glycemic index foods: The white fluffies (e.g. pasta, spaghetti, white bread, bakery products, white rice, potatoes)
- High fructose corn syrup
- Soda and sweetened drinks
- Dairy products (cheese, milk, ice cream)
- Artificial sweeteners including ingredients like aspartame (NutraSweet® and Equal®), sucralose (Splenda®), and saccharine (Sweet 'n Low®)
- Grain-fed meat
- Trans fats
- Environmental toxins like phthalates and pesticides

2 Eat foods with omega-3 and/or take supplements

- Wild salmon, sardines, anchovies and mackerel
- Omega-3 fish oil supplements. EPA + DHA should equal at least seventy percent of the total fish oil listed on the product (triglyceride form)

3 Anti-inflammatory diet/Paleo diet

- Organic vegetables and organic fruits (berries) (3:1 vegetables to fruits)
- Raw unsalted nuts and seeds, grass-fed hormone- and antibiotic-free meat, organic and hormone-free turkey and chicken, eggs, including yolk (from pasture-fed, hormone- and antibiotic-free chickens)
- Healthy fats: avocado, olive oil, raw and unprocessed coconut oil—best for cooking

4 Eat foods that contain lutein and zeaxanthin

- Dark green leafy vegetables (e.g. ½ cup raw spinach, kale and collard greens)
- Goji berries, egg yolks, orange peppers, yellow peppers, oranges, peaches and bananas

5 Drink eight 8-ounce glasses of fluid throughout the day, preferably filtered water

6 Spices

- Cinnamon, rosemary, oregano, garlic powder, Himalayan salt, curcumin, ginger and paprika

7 Vitamin D3: Optimal blood levels (25-hydroxy vitamin D levels 50–70 ng/ml)

- Obtain a serum 25-hydroxy vitamin D measurement prior to determine if you should take a supplement. Obtain these measurements twice per year (summer and winter) during supplementation
- It is important to take vitamin K2, along with vitamin D3, for proper calcium absorption

8 Stress reduction and regular exercise (consult your family doctor)

- Sleep seven to eight hours every night

9 Recommended supplements for ocular nutrition:

- MacuHealth® with LMZ3
- EyePromise® Restore
- Lutein
- Zeaxanthin
- Resveratrol with Pterostilbene
- Astaxanthin

10 Recommended reading:

- "Paleo Diet" by Loren Cordain, PhD (latest edition)
- "The Real Paleo Diet Cookbook" by Loren Cordain, PhD
- "Grain Brain" by David Perlmutter, MD
- "Eat Right For Your Sight" by Jennifer Trainer Thompson and Johanna M. Seddon, MD

Practical Advice for Lifestyle Prevention and Management of Diabetes and Diabetic Retinopathy

BY A. PAUL CHOUS, MA, OD, FAAO

Diabetes mellitus (DM) remains a challenging health care problem throughout most of the industrialized world, with more than 500 million affected and an estimated prevalence of 1.3 billion by 2050 per some reports.[1] Rates of diabetic retinal disease (both diabetic retinopathy [DR] and diabetic macular edema [DME]) also continue to rise, though there is some evidence that disease severity and severe vision loss have lessened in type 1 diabetes as a percentage of that population over the last two decades, presumably due to both better metabolic control and the wider availability of therapies for DR and DME.[2]

Analysis of data from the U.S. Centers for Disease Control and Prevention's Vision and Eye Health Surveillance System estimated that 9.6 million and 1.48 million Americans had DR and vision-threatening DR, respectively, in 2021,[3] and rates of severe vision loss remain unacceptably high and disproportionately affect African, Latino, Pacific Islander, and Native Americans per multiple reports.[4] These statistics underscore not only the importance of preventing and mitigating diabetes complications – including retinal disease – in those with the disorder but also the importance of primary diabetes prevention. To this end, there are some evidence-based lifestyle strategies for the prevention of both diabetes and DR/DME, as well as diabetes remission, that eye care providers can practically and routinely share with patients in clinical practice.

Lifestyle strategies against DM and associated complications encompass a range of interventions, including increased physical activity and dietary modification. They also include less obvious changes such as smoking cessation (smoking is independently linked to type 2 diabetes mellitus [T2DM]), improving sleep quality and quantity linked to better insulin sensitivity, reducing ambient indoor air temperatures to augment thermogenic (calorie-burning) brown adipose tissue, reducing psychosocial stressors that elevate cortisol and promote insulin resistance, increasing serum vitamin D levels to 40 ng/dL in at-risk patients with a BMI < 30 Kg/m^2 and, more broadly, addressing social determinants of health such as community walkability, levels of particulate air and water pollution, added sugar content of packaged foodstuffs, levels of breastfeeding, and food insecurity that are linked to higher rates of diabetes and its complications (see Figure 1). Here are some evidence-based lifestyle strategies for the prevention of diabetes and diabetic retinopathy.

The Diabetes Prevention Program (DPP) and its follow-up, the Diabetes Prevention Program

Outcomes Study (DPPOS), showed that compared to usual care, 150 minutes of weekly walking or metformin significantly reduced and delayed development of type 2 diabetes in high risk patients over 15 years of follow-up.[6] Specifically, walking reduced the overall risk by 56% at year four and 30% at year 10, whereas metformin (850 mg QD) reduced risk about half as well. Exercise was essentially superior to drug at all time points, but patients who were severely obese (BMI > 35 Kg/m^2), younger than 60 years, or who had previously developed gestational diabetes, had relatively better risk reduction with metformin use compared to those who had lower BMI and were older. Although DPPOS subjects in both interventional arms increasingly developed T2DM over time, the delay in diabetes onset reduces the risk of microvascular complications, including DR. No pharmacologic agents for prevention of T2DM have FDA approval, but, in addition to metformin, there is evidence that pioglitazone, acarbose, and glucagon-like-peptide type 1 receptor agonists (GLP-1 RAs) also reduce risk of conversion from prediabetes to T2DM.[7]

Every single health care provider, including optometrists, should discuss diabetes prevention.

Based on results of the DPP, every single health care provider, including optometrists, should discuss diabetes prevention via programs modeled after the DPP with patients having prediabetes (fasting glucose of 100-125 mg/dL or HbA1c of 5.7-6.4%), women with a history of gestational diabetes mellitus, *and* those with established diabetes to mitigate risk of micro- and macrovascular complications. It's relatively easy to find centers offering DPP programs in your community at **https://doihaveprediabetes.org/find-your-program**, but the major features of the program (walking 30 minutes daily and attempted modest weight loss of 5-7%) can be discussed by each of us with our patients.

Going a step further, there is strong evidence that Mediterranean-type diets featuring a wide variety of non-starchy plant foods, regular consumption of tree nuts (walnuts, almonds, hazelnuts), minimization of sugar-sweetened beverages, and regular consumption of marine-sourced long-chain omega-3 polyunsaturated fatty acids (fatty fish) also lower diabetes risk and development of complications, including CV disease and DR.[8] The PREDIMED trial conducted in Spain showed 52% reduced risk of developing T2DM with greater adherence to a Mediterranean-type diet versus control diet over four years of median follow-up,[9] and nearly a 50% reduction in developing sight-threatening DR with a mere two servings of fatty fish per week, after all controls.[10]

What about using diet and weight reduction for T2 diabetes remission, which is generally defined as fasting glucose < 100 mg/dL and HbA1c < 6.5% off of all anti-diabetes medications? The DIRECT trial conducted in the U.K. showed that 46% of T2DM patients achieved remission at two years with an intervention consisting of withdrawal of anti-diabetes and antihypertensive drugs, total diet replacement (825–853 kcal per day formula soup and shake diet for 12–20 weeks), stepped food reintroduction (two to eight weeks), and then structured support for weight-loss maintenance, with 23% of these patients still in remission at five years.[11, 12] Recently, an intervention with Chinese Medical Nutrition Therapy, consisting of six consecutive cycles of 850 Kcal high-fiber/protein gruel daily intake for six days followed by ad libitum diet for 10 days (one cycle) resulted in a mean 13 pounds weight loss at three months and 47%/44% remission of T2DM at three months and 12 months, respectively.[13]

Multiple fasting regimes, including time-restricted feeding (e.g. a

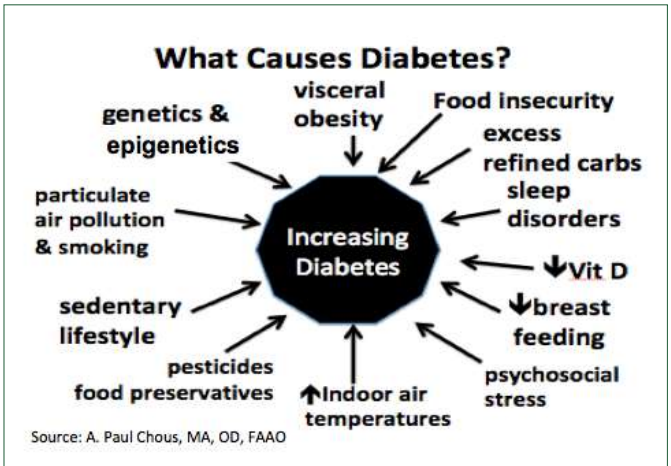


Figure 1. Multifactorial Etiology of the Diabetes Epidemic[5]

feeding window of four to six hours daily) and alternate daily fasting, or ADF, (1,500 Kcal low carbohydrate diet on feeding days alternated with consumption of only water/unsweetened tea or coffee and no caloric intake on fasting days) also have been associated with weight loss in overweight/obese patients and improved insulin sensitivity,[14] the latter strategy having been popularized by the Toronto-based nephrologist, Jason Fung, MD. I now have had 12 obese patients with T2DM (all males) use the ADF strategy with weight loss ranging from 35 to 62 pounds by six months and decreased use/dose of anti-hyperglycemic medications with significant reductions in glycated hemoglobin from baseline (1.7% to 3.0%).

PHOTO CREDIT: gradyreese/Getty Images

Recently, the U.S. Centers for Disease Control and Prevention published a monograph on using various patient incentives to improve diabetes outcomes. The meta-analysis of 19 randomized controlled trials showed that various financial incentives (mean of $270, often spaced out over time) significantly improved mean weight loss (five pounds), and blood pressure (about 2.5 mm Hg, enough to lower stroke risk at a population level about 10%).[15] Prevention is far more cost-effective than treatment, and financially incentivized treatment plans could be employed by insurance companies, health care systems, and even individual providers, especially for socioeconomically disadvantaged patients who are more likely to have poor metabolic control and experience more severe diabetes complications, including children and adolescents, for whom rates of type 2 diabetes are escalating rapidly.

Interestingly, coffee consumption has been linked to reduced risk of T2DM in multiple studies, irrespective of caffeine content. One meta-analysis of observational studies found a dose-response relationship with 30% risk reduction for five cups daily consumption and another 6% reduction per additional cup.[16] The mechanism underlying this protective effect may have to do with polyphenolic content of coffee beans, substances that appear to improve both pancreatic beta cell function and hepatic insulin sensitivity.[17] One of these polyphenols, chlorogenic acid, also decreases VEGF in animal models.[18] Cross-sectional analysis from the 2008–2011 Korean National Health and Nutrition Survey (n = 37,753) showed a 47% reduction in any DR and a 70% reduction in sight-threatening DR with more than two cups daily coffee consumption compared to rare or no consumption in participants under age 65 years, after controlling for confounders like diabetes duration, BMI, and glycated hemoglobin.[19] Clearly, more study in multiple, diverse populations is needed.

Though obesity and abdominal obesity are well-recognized risk factors for the development of T2DM, worldwide econometric analysis has been published showing that added sugar consumption is more strongly associated with type 2 diabetes prevalence at a population level than is obesity.[20] When daily per capita added sugar intake increases 150 Kcal (the equivalent of an extra 12 ounce serving of a sugar-sweetened beverage each day per person), nationwide diabetes levels increase 1.1% based on analysis of 174 countries. This finding requires that patients/consumers be taught to read nutrition labels and identify added sugar content in packaged foodstuffs and for regulatory bodies to limit added sugars for the benefit of public health. The World Health Organization has recommended that added sugars be limited to less than 50 grams per day and, ideally, to less than 25 grams per day.[21] There is some good evidence that high fructose corn syrup (HFCS), in particular, increases de novo lipogenesis and uric acid within the liver, directly contributing to non-alcoholic fatty liver disease (NAFLD), insulin resistance and T2DM.[22] I recommend that all of my patients avoid HFCS whenever possible.

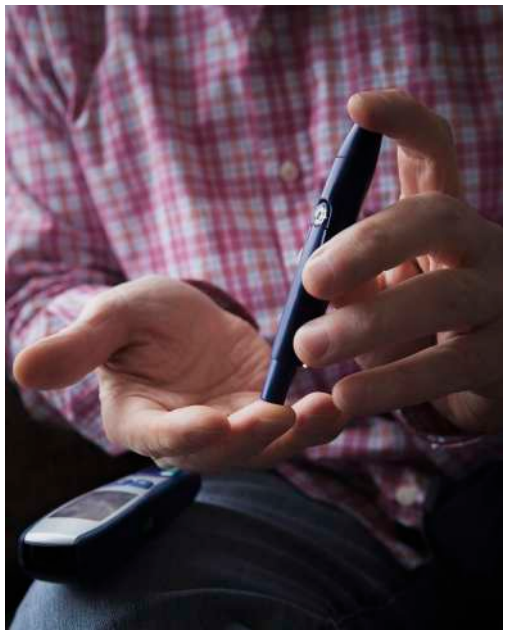
Of course, preventing the onset of diabetes is the singular

best strategy for preventing DR in general and sight-threatening diabetic retinopathy (STDR) specifically. As for secondary prevention, every prospective trial has shown that better blood glucose control is associated with lower risk of DR and that early, good glucose control provides a "legacy effect" against future development of severe DR despite worsening diabetes control over time (so-called "metabolic memory"). However, there are now multiple lines of evidence suggesting that once patients develop non-proliferative DR, severe and even episodic hypoglycemia increases the risk of progression to STDR.

The Freemantle Diabetes Study Phase II conducted in Western Australia found that hospitalization for severe hypoglycemia was the single most predictive variable for vision loss in patients with T2DM, with a 5.6-fold hazard ratio.[23] In a nationwide cohort of more than 71,000 privately insured patients in the U.S. with T2DM, the single most predictive factor for the development of PDR at five years was use of exogenous insulin (HR = 3.6), whereas HbA1c > 9% merely doubled the risk.[24] Moreover, insulin use has been shown to be the single biggest risk factor for severe hypoglycemia, with more than 95% of T2DM patients on insulin therapy having objective hypoglycemia (glucose < 56 mg/dL) when assessed by continuous glucose monitoring devices.[25] Consistent with this hypothesis, requisite use of exogenous insulin in all persons with type 1 diabetes and associated hypoglycemia, in addition to more profound hyperglycemia, may contribute to higher prevalence of DR in these patients.

Hospitalization for severe hypoglycemia was the single most predictive variable for vision loss in patients with T2DM.

In the PANORAMA trial, better glycemic control (HbA1c < 7.8%), an indirect surrogate biomarker for probability of hypoglycemia, increased the odds of progression to a vision-threatening complication in high-risk patients (having moderately severe or severe NPDR at baseline) compared to subjects in two higher tertiles of glycated hemoglobin.[26] Perhaps most compelling, recent analysis of human retinal tissue showed that episodic hypoglycemia lasting only 15 minutes up-regulated mRNA expression of hypoxia-inducible factor 1-a and GLUT1 by Muller cells in ischemic retina, known antecedents to both PDR and DME, by more than 100-fold.[27] These findings are totally consistent with the so-called "diabetic retinopathy re-entry phenomenon," wherein patients with poor glucose control and NPDR experience sudden worsening of disease with large, rapid correction of hyperglycemia, a phenomenon well documented with initiation of insulin therapy[28] and, more recently, the highly potent GLP-1 drug, semaglutide, particularly when coupled with insulin or sulfonylurea therapy that potentiate its hypoglycemic effects.[29]



The apparent and largely unrecognized importance of hypoglycemia in the genesis of diabetic retinopathy and other complications, including cognitive decline and even higher mortality,[30, 31] underscores the need for therapeutic strategies to provide consistent, stable euglycemia (normal blood glucose) without provoking severe low blood sugars. For example, the use of available ultra-long-acting insulins such as degludec [Tresiba, Novo Nordisk]) that limit hypoglycemia and future development of glucose-dependent insulin that only activates when glucose is elevated; intake of low-glycemic index foods that require less insulin to correct hyperglycemia and thereby lower risk for hypoglycemia due to dose miscalculation and variable absorption of subcutaneous insulin; wider use of drugs less likely to cause hypoglycemia; far more use of continuous glucose-monitoring systems that give patients real-time feedback about current and near-term glucose levels. The bottom line is that initiation of DR

PHOTO CREDIT: REB Images/Getty Images

requires hyperglycemia, but when ischemic retina is subjected to low blood sugar levels, DR may actually and substantially worsen – so we should all use caution when reflexively counseling patients with NPDR and their other health care providers about achieving "tighter blood sugar control" with agents most highly associated with acute hypoglycemia (insulin and sulfonylureas).

It's an apt health care truism that *prevention beats cure*. By counseling our patients about lifestyle strategies to prevent or delay type 2 diabetes onset, as well as strategies to prevent severe diabetic retinopathy if/when either type 1 or type 2 diabetes develops, optometrists and other health care providers can help turn the tide against these increasingly prevalent conditions. ■

A. Paul Chous, MA, OD, FAAO, has a practice emphasizing diabetes eye care and education in Tacoma, Wash. He is Adjunct Professor of Optometry at Western University of Health Sciences in Pomona, Calif., and writes/lectures frequently on diabetes.

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Can a Healthy Diet Affect Open-Angle Glaucoma?

BY JULIE POTEET, OD, MS, CNS, FOWNS

Poor diet is the leading cause of mortality in the United States, causing more than half a million deaths per year.[1] In a 2019 article in *The New York Times,* **"Our Food Is Killing Too Many of Us,"** Tufts Friedman School of Nutrition's Dr. Dariush Mozaffarian and former secretary of agriculture Dan Glickman make the argument that improving American nutrition would make the biggest impact on our health care. The United States government is waking up to this knowledge. On May 27, 2020, the National Institutes of Health released its first ever strategic plan to accelerate nutrition research with the emphasis on the role of dietary patterns for optimal health. Americans are becoming sick and tired of being sick and tired. As a practitioner, there is not a day that goes by without a patient asking what lifestyle changes can help with their treatment.

Glaucoma is the leading cause of irreversible blindness worldwide, with primary open-angle glaucoma (POAG) constituting most cases. Factors other than elevated intraocular pressure (IOP) have been implicated in the pathogenesis of glaucoma. Oxidative stress, axonal transport failure, neurotrophic factors, and nutritional factors have also been implicated in the pathogenesis of retinal ganglion cell (RGC) loss.[2, 3, 4, 5, 6] There is a growing interest in non-pharmacologic and lifestyle changes in the management of eye disease.

Oxidative Stress

Glaucoma is a multi-faceted disease where many pathological mechanisms contributing to glaucomatous neurodegeneration are caused by, lead to, or contribute to oxidative stress, inflammation, reactive gliosis, and apoptosis.[7, 8, 9, 10] Of all external factors in our environment, diet is one of the largest influences on inflammation and oxidative stress. Low levels of ocular or systemic antioxidants are associated with POAG and more severe visual field loss.[11, 12, 13] In clinical studies, a significant association between low serum levels of antioxidants, including vitamin C and D, and POAG have been reported.[14, 15]

In a comprehensive review paper published in the *European Journal of Ophthalmology* in 2021,[16] the authors conducted a literature review of the effect of dietary modification and antioxidant supplementation on intraocular pressure and open-angle glaucoma. They concluded that overall, experimental and animal studies thus far have shown promising results regarding the potential of antioxidants to control the oxidative environment in ocular hypertension and glaucoma. However, results from large population-based prospective cohorts and randomized clinical trials have shown mixed results. Based on the level of evidence thus far, the authors concluded that it is not yet possible to recommend a specific adjuvant treatment protocol.[16] However, the following are evidence-based recommendations that have been shown to be beneficial adjuvants to standard glaucoma therapies.

OMEGA-3 FATTY ACIDS:

In multiple studies, feeding animals with omega-3 fatty acid-enriched diets over three to six months correlated with a reduction of IOP via improving aqueous outflow, the attenuation of stress response in retinal cells, and

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the prevention of retinal cell loss following IOP elevation.[17, 18, 19, 20] The National Health and Nutrition Examination Survey (NHANES 2005-2008) data, a cross-sectional survey involving 3,865 participants from the United Sates, has shown that high dietary consumption of eicosapentaenoic acids (EPA) and docosahexaenoic acids (DHA) from omega-3s are correlated with a lower probability of glaucomatous optic neuropathy.[16] Oral omega-3 supplementation for three months significantly reduced IOP in normotensive adults in a recent study, and this reduction is thought to be due to increasing aqueous outflow and anti-inflammatory properties of omega-3s.[21] Omega-3s have neuroprotective effects and support ocular microcirculation.[21]

VEGETABLE AND FRUIT INTAKE:

Research has shown that a diet high in green leafy vegetables is inversely related to the risk of POAG.[22] The protective effect is thought to be due to the abundance of nitrates in green leafy vegetables and the production of nitric oxide that is critical in the pathophysiology of POAG. Nitric oxide is a direct regulator of IOP, and it has been shown to be neuroprotective. It also regulates blood flow and vascular tone. Other foods that have been shown to increase nitric oxide are the flavonoids in dark chocolate, beets, garlic, pomegranate juice, citrus fruits, and watermelon.

MIND DIET:

The MIND diet is the Mediterranean-DASH Intervention for Neurodegenerative Delay diet that was developed as a strategy to promote healthy cognitive aging. It is a combination of the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet and it has been shown to reduce the incidence of Alzheimer's disease and cognitive decline.[23] The MIND diet contains brain healthy foods such as green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, fish, poultry, olive oil, and moderate red wine. It limits red meat, butter and stick margarine, cheese, pastries and sweets, and fried/fast foods. The MIND diet has been shown to be neuroprotective in POAG independent of IOP-lowering effects.[23]

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COENZYME Q10:

Coenzyme Q10, also known as ubiquinone, is a vitamin-like compound found in every cell of the body. It plays a vital role in the production of energy within the mitochondria, which are the powerhouses of the cell. It also functions as an antioxidant and is neuroprotective. In glaucoma, coenzyme Q10 has been studied for neuroprotection and has been shown to reduce oxidative stress, improve mitochondrial function, and reduce inflammation.[24, 25] It is important to note that roughly 60% of older Americans are on statin therapy to lower cholesterol and protect against heart attack and stroke. Statins have been shown though to reduce levels of coenzyme Q10 in the body by as much as 40%,[26] so patients may want to incorporate coenzyme Q10 in their regimen. Good food sources of coenzyme Q10 include organ meats, fatty fish, soybeans, vegetables, nuts, and seeds. Coenzyme Q10 can also be taken in supplement form.

GINKGO BILOBA:

Ginkgo biloba is a plant native to China. The leaf contains about 20 different types of flavonoids and has been studied for neuroprotection in glaucoma. Ginkgo has been shown to have antioxidant and vascular effects. Ginkgo has been shown in some studies to slow visual field progression in normal tension glaucoma patients.[27, 28] However, follow-up studies with the same design failed to replicate the findings. More studies are needed to determine whether ginkgo is an effective adjuvant treatment in POAG.

SAFFRON EXTRACT:

Increasing evidence from both experimental models and clinical studies in patients supports the neuroprotective effect of saffron components in neurodegenerative conditions due to its anti-inflammatory, anti-apoptotic, and antioxidant properties. It has been shown to reduce microglial activation, regulate the production of proinflammatory cytokines, and prevent ganglion cell death.[29] While more

evidence is needed, this is on the horizon for future adjuvant treatments for POAG.

Mitigating the effects of oxidative stress and inflammation in glaucoma through diet and lifestyle factors represents exciting new avenues for research and clinical practice. As the AREDs trials showed us that nutrients can mitigate the course of age-related macular degeneration, specific nutrient protocols for glaucoma therapy may be next on the horizon. In the meantime, patients can be encouraged to increase vegetable and fruit intake, fatty fish and omega 3s, nuts, seeds, berries, polyphenols, antioxidants, and micronutrients. ■

Dr. Julie Poteet, OD, MS, CNS, FOWNS, graduated from The New England College of Optometry and then completed a residency in primary care and ocular disease at the VA Medical System in Boston. At the VA, Dr. Poteet became interested in why some veterans seemed to age so differently from their peers and began questioning what lifestyle factors have the greatest impact on health and vitality. She then went on to complete a Master of Science in Human Nutrition and Functional Medicine. After earning her Master's Degree, she then completed the requirements to become a Certified Nutrition Specialist in 2015, becoming one of the first ODs to attain CNS certification. Dr. Poteet served as Vice President of the Ocular Wellness & Nutrition Society (OWNS) for six years under her mentor Dr. Stuart Richer, and she served as President of OWNS for three years. She has lectured extensively on the microbiome and immune system dysfunction. She works in Atlanta, where her office is a Macular Degeneration Center of Excellence. She is a member of the American Nutrition Association, formerly the American College of Nutrition. Dr. Poteet is passionate about carrying on the legacy of her mentor, Dr. Stuart Richer, whose mantra "repair the roof before it starts raining" is an excellent metaphor for using lifestyle and nutrition to mitigate the course of disease.

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The Eye is a Window to the Heart: Optometry's Role in Cardiovascular Disease Detection and Prevention

BY DOROTHY L. HITCHMOTH OD, FAAO, ABO, ABCMO

Cardiovascular disease (CVD) is the leading cause of mortality globally and is gaining in worldwide prevalence.[1] The top 10 CVD risk factors include unhealthful nutrition, lack of exercise, hyperglycemia, hypertension, obesity, age, smoking, kidney dysfunction, and familial hypercholesterolemia.[2] These facts are not elusive to doctors of optometry, however, our role in early detection and prevention must evolve to meet the demand for expertise given the aging population, doctor shortage, and faltering healthcare system.[3] Our role in prevention of CVD is important given our direct view of the body's vasculature. Emerging science is further defining the sensitivity of ocular biomarkers in CVD prediction, lending an opportunity to engage our patients, and positively impact public health outcomes Atherosclerotic cardiovascular disease (ASCVD) is the most prevalent form of CVD, and broad public health studies and education are largely focused on ASCVD. Also, eye care providers currently provide nutrition and supplement recommendations to those with age-related macular degeneration, which is linked to ASCVD, and research has shown that lutein and zeaxanthin, which are often prescribed "eye" nutrients provide significant **cardio-protective benefits.**

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The Eye-Heart Link Risk Association

The retinal-vascular-choroidal complex has high oxygen demand that requires well-regulated blood flow.[4] Coronary artery disease is known to cause endovascular mechanical stress resulting in glycocalyx degradation that ultimately leads to end-organ capillary impairment and measurable damage in areas of the body such as the retina.[5] Also, retinal endothelial cells are more vulnerable to oxidative stress because of the natural imbalance between superoxide and superoxide dismutase, which in unstressed tissue keep reactive oxygen species (ROS) in check.[4] The presence of excess ROS is also implicated in ASCVD and further compounds retinal endothelial damage, making it no surprise that the eye-heart link risk association should be further correlated.[6]

Understanding individual and population risks for ASCVD is important for understanding how to best counsel patients who have traditional risk factors as well as ocular biomarkers. Risk factor scoring has been a decades-long endeavor starting with the well-known **Framingham Heart Studies.** Risk scoring has evolved into a cross-specialty global research endeavor with the latest scoring tool known as the **Pooled Cohort Risk Estimator Plus.** This scoring tool is used by treating providers to refine individual patient advice from pooled cohort data. In other words, it helps providers evaluate individual patient profiles in order to determine the potential benefits from lifestyle modification versus pharmaceutical treatment or both in both primary and secondary prevention medical advice. The American

Society for Preventive Cardiology and the American Heart Association experts systematically review the scientific literature and publish clinical practice statements that are broadly referenced in health care.[7] Risk factor analysis drives these current care algorithms. However, primary prevention advice closely follows the advice that optometrists and ophthalmologists often give patients regarding prevention of vision loss from conditions such as retinal vascular emboli and thrombosis, macular degeneration, non arteritic ischemic optic neuropathy, and normal tension glaucoma, to name a few.[8, 9, 10, 11] Prevention guidelines published by our colleagues in *The American Journal of Preventive Cardiology* help parse patients into low, moderate, high risk, and very high-risk profiles. For patients at low risk for ASCVD, lifestyle recommendations are often the primary treatment. There are other factors that can help refine individual risk for ASCVD, but there are general population risks that all providers caring for the aging patient should understand in order to counsel and refer patients appropriately. For example, lifestyle recommendations are something that all clinicians can work to disseminate.

The ophthalmic literature provides evidence that links certain eye conditions to CVD risk, but eye care providers need to understand the overall risks associated with ASCVD in order to provide patients with a lifetime of advice regarding primary prevention of ASCVD because this is what also prevents vision loss and eye-related morbidity.

Risk factors for ASCVD include a family history of premature ASCVD, primary hypercholesterolemia, metabolic syndrome, chronic inflammatory conditions, and chronic kidney disease. See Figure 1. Identifying individuals at risk for ASCVD requires both physical and laboratory investigation for individual stratification. These measures may be unavailable or elusive to those outside hospital-based practice, and, for example, it is important to understand that calcium artery scoring is used to further stratify individual ASCVD treatment decisions for statin therapy.[7] However, on the eye care front, medical and social history often provide information that combined with ocular biomarkers may help drive more appropriate testing and early identification of ASCVD for those who are asymptomatic or undiagnosed.

Risk Enhancing Factors for the Clinician-Patient Discussion.

Family history of premature ASCVD; (males, age <55 y; females, age <65 y)

Primary hypercholesterolemia (LDL-C, 160-189 mg/dL [4.1- 4.8 mmol/L]; non-HDL-C 190-219 mg/dL [4.9-5.6 mmol/L])*

Metabolic syndrome (increased waist circumference, elevated triglycerides [>175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis)

Chronic kidney disease (eGFR 15-59 mL/min/1.73 m2 with or without albuminuria, not treated with dialysis or kidney transplantation)

Chronic inflammatory conditions such as psoriasis, RA, or HIV/AIDS

History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as pre-eclampsia

High-risk race/ethnicities (e.g. South Asian ancestry)

Lipid/biomarkers: Associated with increased ASCVD risk

Persistently elevated, primary hypertriglyceridemia (≥175mg/dL);
Elevated high-sensitivity C-reactive protein (≥2.0 mg/L
Elevated Lp(a) A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥ 50 mg/dL or ≥125 nmol/L constitutes a risk enhancing factor especially at higher levels of Lp(a)
Elevated apoB ≥130 mg/dL - A relative indication for its measurement would be triglyceride ≥ 200 mg/dL. A level ≥ 130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk enhancing factor

Figure 1. https://pubmed.ncbi.nlm.nih.gov/35342890/

Eye Disease and Cardiovascular Disease

There are many readily identifiable eye conditions such as normal tension glaucoma, age-related macular degeneration, ischemic optic neuropathy, retinal thrombosis and embolism, hypertensive retinopathy, and diabetic retinopathy that have been linked to CVD.[12–21] CVD risk in adults with vision loss is higher than those without.[22] These disease states and their associations have been well described in the literature and warrant appropriate referrals to a number of sub-specialists to include cardiology, internal medicine, primary care, vascular surgeons, and neurology. Eye care professionals are well versed in the trajectory and treatment of these diseases, but there are important ocular biomarkers that do not represent classified eye diseases that may have important implications in the early detection of asymptomatic CVD. Understanding the power of these markers and how to measure them promises to lead to improved patient quality of life and morbidity and mortality outcomes.

Ocular Biomarkers and Coronary Atherosclerosis

Ocular biomarkers of cardiovascular risk are not elusive to eye care providers. Research has shown the certain features of the retinal vasculature correlate to CVD risk and events. Clinically observed retinal arteriolosclerosis (hyaline sheathing), aterio-venous nicking, banking, dilation, and other retinal vascular abnormalities have been shown to be associated with CVD for decades.[11,23 24–27] These anatomical correlates are being measured in increasingly sophisticated ways and continue to support a strong eye-heart disease predictive relationship. Artificial intelligence combined with a variety of retinal imaging techniques such as retinal photos, ocular coherence tomography, hyperspectral retinal imaging, and adaptive optics have sharply increased the sensitivity and specificity of retinal findings to heart disease.[28–32] For example, retinal fractal dimensions such as arteriolar curvature tortuosity and retinal arteriolar caliber were compared to coronary artery angiograms in the Australian Eye Heart Study. Straighter arterioles were associated with greater odds of coronary artery disease (CAD) in men, and narrower venular branching angle was associated with CAD in women. There were ranges of combined retinal vessel measurements that were of further statistical significance in correlation to CAD.[33] Observational studies continue, and new retinal microstructures are being described in OCT imaging to **include retinal ischemic lesions.**

These findings have been associated with increased odds of CVD, and their number positively correlated with the increased 10-year ASCVD risk score.[34] There is also strong evidence from a large population-based study of more than 65,000 retinal photos whereby image extracts of retinal arteriolar and venular width were analyzed by Quartz-enabled artificial intelligence. Authors suggest that this form of vasculometry may predict cardiovascular or circulatory mortality just as accurately as conventional blood work and blood pressure.[35]

Moreover, a recent systematic review of over 42 publications, spanning 20 years, reveals evidence that certain retinal microvasculature features serve as collective biomarkers for cardiac disease as well as predict future risk of cardiac events. Retinal vascular diameter, tortuosity, and branching features are shown to be reliable features of interest in the plethora of studies analyzed.[36]

Even smartphone-based systems for analyzing retinal images have been validated in studies. Xu et al. demonstrated that retinal images uploaded to a smartphone-based app from a variety of sources that include well known image databases such as **DRIVE** (Digital Retinal Images for Vessel Extraction) and **STARE** (Structured Analysis of the Retina), confirm that a vessel segmentation algorithm is a statistically comparable, quantitative methodology that provides reliable, equivalent measures of retinal vascular abnormalities. The detection of retinal vascular abnormality was similar whether or not images were taken by a smartphone or state-of-the-art fundus camera.[37] This study, as well as other similar studies, demonstrate that point-of-care prediction of both eye and systemic vascular disease is possible. See Figure 2.

Similarly, SD-OCT images reveal biomarkers not associated with any particular eye condition that may predict occlusive coronary disease. Generalized choroidal thinning, retinal thinning, and loss of vascular density in the central retina are specific features that have been associated with higher rates of myocardial infarction and three-vessel (coronary) disease.[38]

Non-vascular retinal biomarkers have a role in CVD prediction as well. A recent study revealed that a specific form of subretinal drusenoid deposits (SDD) are strongly associated with co-existent high-risk vascular disease. In fact, AMD patients with this particular SDD formation and cardiovascular diseases and stroke were nine times more likely to have SDD than those without, making SDD a potential strong biomarker of CVD risk and disease identification.[9]

Novel Ocular Biomarkers in CVD Risk Assessment

Neuroscience and cardiology are also converging on the fact that light exposure through the retina has a trans vascular effect on cardiac function and overall health, furthering the notion of the brain-retina-heart link.[39] Non-imaging-forming retinal ganglion cells are responsible for controlling various functions in the brain that drive these associated autonomic functions. There are numerous pathways through the brain that include travel through the suprachiasmatic nuclei and the lateral geniculate nucleus. These structures are responsible for circadian rhythm, sleep cycles, and cardiac function.[40–49] Disruption of the sleep cycle is a risk for CVD. Stud-

ies even show that control of light through the pupil can have neuro and cardio modulating effects.[50–54] These effects can be measured via pupil activity and may help add to the overall identification of CVD by novel biomarker measurements.[51, 52]

Given the current plethora of evidence, it is plausible that retinal imaging analysis and neuroocular functional assessment may become the most powerful, inexpensive, accessible tool for predicting cardiovascular disease. In fact, the evidence is so compelling that the National Heart, Lung, and Blood Institute of the National Institutes of Health convened a multi-specialty virtual workshop in October 2022 in order to review the current state of knowledge about retinal biomarkers obtained from retinal imaging. They emphasized that systemic hypertension is a major risk factor for CVD, which includes heart disease, peripheral artery disease, and vascular dementia. The group outlined a plan to better understand the link between retinal vasculature and CVD because "compared to cardiovascular imaging, ocular imaging is easier to perform, less expensive, non-invasive and can provide high resolution images of retinal blood vessels."[55]

Ophthalmic imaging has the potential to become an economical, point-of-care, risk-scoring tool that streamlines care and stratifies individual risk of heart disease at a high level of sensitivity and specificity. Perhaps, ASCVD and CVD risk and triage will start with an eye exam. Future research promises to further define the role of the eye care professional in the management of the number one cause of morbidity and mortality in the world. This does not preclude educating patients about how to delay, prevent, or manage CVD according to primary prevention tactics that include smoking cessation, control of blood pressure, weight, blood glucose, and unhealthy fat and food intake. The simplest chairside advice for preventing CVD is to educate your patient on the benefits of the traditional Mediterranean Diet. This diet has been studied the world over, and there is a large, strong, plausible, and consistent body of available prospective evidence to support its benefits on cardiovascular health.[56] Optometrists interface with over 200 million people in the United States, and we have an obligation to perpetuate the life-saving advice promulgated by Hippocrates, "Let food be thy medicine." ■

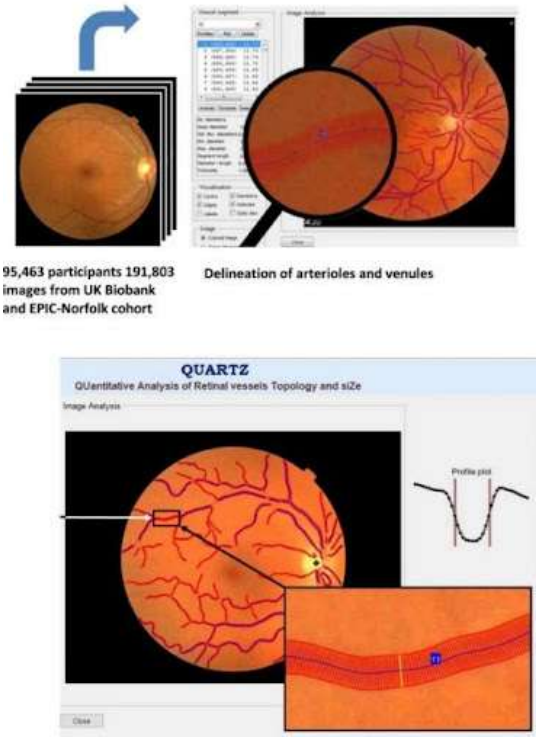

Figure 2.
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The Rising Need For a Holistic Approach To Medication Management: Drug-Nutrient and Drug-Herb Interactions

BY LARA ZAKARIA, PHARMD, MS, CNS, CDN, IFMCP

According to the **Centers for Disease Control and Prevention (CDC), 71.9%** of physician office visits in the United States result in drug therapy.[1] Furthermore, the **CDC reports that 7 in 10 U.S. adults between 40-79 years old** had used at least one prescription drug in the previous 30 days.[2] At the same time, the National Center for Health Statistics' **National Health and Nutrition Examination Survey conducted for 2007–2018 reports that 57.6% of U.S. adults used dietary supplements** in the past 30 days, with the number of supplements increasing with increasing age.[3]

In our collective mission to improve patient outcomes, it's essential to consider the millions of people on prescription medications and the physiological and financial impact of medication burden. When used responsibly, medication can have a tremendous and often life-saving impact on disease state management. We have to also consider **patients who express dissatisfaction with their medication** due to inadequate response, side effects, costs, **among other reasons,** which drives them to seek alternatives.[4, 5] As a result, there's a demand for a more holistic approach to medication management within the context of a more integrative lifestyle medicine framework.

This paradigm shift invites us to take a deep dive into the intricate world of drug-herb interactions (DHI), drug-induced nutrition depletion (DIND), and drug-nutrient interactions (DNI). As we forge a path toward a more holistic approach to medication management, we recognize these interactions hold the key to unlocking safe and effective nutraceutical use. However, navigating these interactions requires deftness of understanding and a keen eye for detail – precisely where specialized pharmacists can lead the way as part of a collaborative care team.

The Rising Need for a Holistic Approach to Medication Management

As modern-day health care evolves, the role of pharmacists is rapidly transforming, making them strategic allies on the frontlines of personalized medication management. With the rise in chronic disease along with increasing awareness of the importance of lifestyle medicine, it has become **crucial for health care providers to integrate lifestyle medicine components into practice.** This approach supports implementation of evidence-based lifestyle components, including nutrition, physical activity, sleep, stress management, and social connections. To effectively integrate lifestyle medicine into clinical practice, health care professionals must effectively adopt this holistic approach. **Clinicians must also consider factors such as patient's individual needs, preferences, and objectives** that often include use of nutraceuticals.[6]

Pharmacists have been chameleons for centuries, evolving their role to fit the needs of the times. During the earliest days of medicine, **apothecaries served as healers,** using their vast knowledge of herbs and natural substances to create remedies for various ailments.[7] They were the primary source of medical advice and served as the community's herbalist, utilizing their knowledge of botany and chemistry to formulate treatments.

As medicine advanced, the role of the pharmacist would evolve into more specialized areas, including chemists, toxicologists, drug information specialists, and pharmaceutical experts, providing valuable advice on medication use, safety, and interactions. The field of **pharmacognosy, which involves the study of medicinal plants** for the development of pharmaceuticals, is over 200 years

old, further emphasizing the pharmacist's roots in understanding the complex relationship between nature and medicinal development.[7, 8]

Whether they're called apothecaries, chemists, druggists, or pharmacists, they have always used their extensive knowledge of drug therapy in collaboration with other clinicians to ensure safe and effective medication use. There's no doubt that the next evolution of the pharmacist's role will reflect the changing needs of society and the health care system, responding to new challenges and opportunities in order to return to our nutraceutical roots.

Growing Public Interest in Supplements

In recent years, **there has been a noticeable surge in public interest in dietary supplements.** As people become more proactive about their health, many are turning to natural products and nutraceuticals as a means to prevent disease and promote overall wellness. This trend is partly driven by the **growing body of research supporting the health benefits of certain herbs, vitamins, and minerals** and growing public interest post-COVID-19 pandemic in particular.[9, 10]

However, while supplements can offer numerous health benefits, they are not without risks. For example, many people are unaware of the potential interactions between dietary supplements and prescription medications, which can lead to adverse effects or compromised drug efficacy. We can organize these interaction risks into the following categories:

1. **Drug-herb interactions (DHI)**
2. **Drug-nutrient interactions (DNI)**
3. **Drug-induced nutrient depletions (DIND)**

The rising interest in supplements means more potential opportunities to educate and counsel patients on proper use. By integrating supplement counseling into their practice, clinicians can provide valuable services that not only enhance patient safety but also ultimately contribute to better health outcomes.

Clinical Opportunities in Nutraceutical Use

By understanding the intricacies of drug-nutrient and drug-herb interactions, clinicians can play a pivotal role in enhancing patient outcomes. For example, proton pump inhibitors **(PPIs), often used for heartburn and acid reflux, can lead to nutrient depletions over time including most notably magnesium and vitamin B12.**[11] This is a great example of DIND and an opportunity to assess nutritional status and counsel on supplement needs.

Examples of DINDs by mechanism

Drug or Class	Proposed Mechanism	Nutrient Depleted
Proton Pump Inhibitors (PPIs)	Inhibit/reduce absorption	Magnesium, B12
Statins (HMG-CoA inh)	Inhibit synthesis	CoQ10
Metformin	Blocks absorption across GI lumen	B12, folate
ACE inhibitors	Increased excretion	Zinc

Table 1: Examples of DINDs by mechanism[12]

DRUG-INDUCED NUTRIENT DEPLETIONS (DIND):

DIND is defined as the reduction or depletion of nutrients in the body caused by the intake of certain medications.[11, 12] Unfortunately, DIND are not often recognized when medications are prescribed, with the exception of major issues (the need to supplement folic acid with methotrexate is one example).[12] As a result, nutritional supplements may not be included in most medication counseling encounters. Besides the PPI example given above, other good examples include:[12]

- **Depletion of coenzyme CoQ10** with statins (HMGCoA-Inh)
- **Metformin,** which inhibits the absorption of vitamin B12 and folate across the gastrointestinal lumen membrane
- **Hypertension medications,** ACE inhibitors, increase the excretion of zinc leading to depletions of the mineral

It's worth mentioning that there are chronic conditions that have special nutritional concerns. These conditions might warrant their own nutraceutical interventions and add physiological stress, necessitating personalized nutritional interventions. Examples include **magnesium, chromium, zinc, fish oil, and polyphenols for diabetes and cardiovascular disease** (CVD).[12, 13]

DRUG-NUTRIENT INTERACTIONS (DNI):

Similar to DIND, we can also assess the DNI as a whole. The term **DNI refers to physical, physiological, or pathophysiological relationships between a drug and a nutrient.**[12] As many as **48% of patients taking dietary supplements concomitantly with prescription drugs** have been found to be at risk for a DNI.[12]

These interactions can be complex and can impact the absorption, distribution, metabolism, and excretion of both the drug and the

nutrient. Some examples of this bi-directional interaction includes fatty foods that increase drug absorption of some lipid soluble drugs, alterations of the microbiome and vitamin K deficiency with antibiotic use, and the formation of irreversible or insoluble complex between certain nutrients and medications, resulting in reduced bioavailability (i.e. iron or calcium and fluoroquinolones).[12, 14, 15] Some of the most notable interaction involves the enzymatic induction or inhibition of CYP450 enzymes by certain foods (i.e. grapefruit inhibits CYP3A4, and CYP1A2 is induced by cruciferous vegetables and barbecued or charbroiled).[12, 14, 15] There are **various physiological factors that may impact the type and intensity of DNIs,** including patient-related variables such as age, sex, comorbidities, nutritional status; and drug- nutrient-associated factors, including route of administration, nutrient status, and pharmacological/toxicological profile of the drug.[15]

Understanding these interactions and layering with integrated health data evaluation (for example, family history, medical and metabolic data, -omics profiles) for potential nutritional depletions is critical if we aim to prevent disease associated with disruption of nutritional homeostasis.[15] This is a practical and necessary starting point toward personalized lifestyle interventions that address the needs of the individual patients and inform appropriate drug prescribing and nutritional advice. Furthermore, when we **minimize DNIs we can potentially reduce polypharmacy, health-care utilization and costs, and enhance patient health outcomes.**[15]

DRUG-HERB INTERACTIONS (DHI):

Apart from DNIs and DINDs, another critical aspect to consider is **drug-herb interactions (DHI).** These interactions occur when a patient uses both prescription medications and herbal supplements, which can lead to changes in the effectiveness or safety of the drug.[16] For instance, the herb **St. John's Wort is known to interact with numerous medications,** potentially leading to reduced effectiveness of the drug or increased risk of side effects due to induction of CYP3A4 and P-glycoprotein. This results in **interactions of many drugs** including antihypertensives, non-steroidal anti-inflammatories (NSAIDs), oral contraceptives, immunosuppressants, and HIV medications. Furthermore, the herb has a similar mechanism to serotonin-reuptake inhibitor antidepressant medication and may increase risk of serotonin syndrome as a result. [16, 17, 18]

Examples of Drug-Herb Interactions (DHI)

St. John's Wort *(Hypericum perforatum)*	*Ginko Biloba*	Ginseng *(Panax ginseng)*
• **Reduces the plasma concentration of MANY drugs** • **Antidepressants** • Antihypertensives • Bronchodilators • NSAIDs • Oral contraceptives • Statins • Benzodiazepines • Immunosuppressants • HIV protease inhibitors	• **Drug candidates for potential interactions** • **Anticoagulants** • **Antiplatelets** • Anticonvulsants • Antidiabetes drugs	• **Drug candidates for potential interactions** • Immunosuppressants • Hypoglycemic agents • Anticoagulant/ antiplatelet drugs • **Additive effects:** • May increase blood pressure, so is not advisable in patients with hypertension • Caffeine with ginseng combination increases GI irritability

Table 2: Examples of DHI[24]

Interactions between **herbs and medications are also influenced by various factors,** including bioindividual factors, pharmacokinetics, the quality and bioactive constituents of the product used, and of course, the type of the interaction that can be classified as additive, synergistic (amplified), or antagonistic.[16] Although we often think of risk of injury or therapeutic effectiveness, the synergistic effects of certain combinations of drugs and herbs might be exploited to improve the benefits of prescribed medications. For instance, **supplementing with curcuminoids** and **resveratrol alongside NSAIDs** can enhance pain relief and reduce inflammatory markers, while reducing the risk of side effects.[19, 20]

The Limitations of Research Data

One of the challenges in the field of nutraceutical safety is the lack of robust research data. Most of the **available evidence on DIND, DNI, and DHI is based on in vitro studies or animal models, and human clinical trials are sparse.**[21] Furthermore, the **bioactive components, genomics, metabolomics, and microbiome impact** of nutritional and herbal products are not fully understood, adding another layer of complexity to the evaluation of safety and effectiveness.[22, 23] It is critical to fully understand these interactions, ongoing research and advancements in pharmacognosy and pharmacogenomics, as they intersect with nutrigenomics.[22, 23] Therefore advocacy for expanded research in this field can pave the way for more informed and **personalized nutrition** and medication management strategies.[23]

Conclusions and the Collaborative Care Team

The rising demand for a more holis-

tic approach to medication management underscores the need for a comprehensive understanding of the intricate interplay between drugs, nutrients, and herbs. As the health care landscape continues to evolve toward a more patient-centric model, the integrative collaborative care team model is becoming increasingly critical. In addition to their traditional responsibilities, pharmacists can work collaboratively with other health care professionals, including physicians and nutritionists, to provide comprehensive and personalized medication management that includes nutraceutical management. This collaborative approach not only enhances patient outcomes but also fosters a more holistic approach to health care. By expanding and leveraging expertise in DIND, DNI, and DHI, pharmacists can guide patients toward safe and effective nutraceutical use, and collectively as clinicians can be a part of the ongoing evolution of health care. ■

Dr. Lara Zakaria, PharmD, MS, CNS, CDN, IFMCP, is a pharmacist and nutritionist with a focus on implementing solutions for functional medicine and personalized nutrition. A graduate of the Ernest Mario School of Pharmacy at Rutgers University (BSpharm) and the University of Colorado Skaggs College Of Pharmacy (PharmD), she spent 20 years in community pharmacy practice. After developing an interest in nutrition, she earned a MS in Nutrition from the University of Bridgeport and subsequently qualified as a Certified Nutrition Specialist (CNS) as well as an Institute for Functional Medicine Certified Practitioner (IFMCP). Dr. Zakaria's practice focuses on a multidisciplinary approach working both one-on-one with patients as well as creating implementation tools and systems for scale. She is also adjunct professor of nutritional biochemistry and therapeutics at the University of Bridgeport, faculty at George Washington University, as well as guest instructor for Functional Medicine at LECOM College of Pharmacy. She has served as mentor and supervisor for CNS and pharmacy students. Dr. Zakaria is passionate about gut health and the prevention and reversal of metabolic, allergic, and autoimmune disease. There's power in community, working with pharmacy professionals, nutritionists, and other clinicians to leverage their unique expertise to amplify the message of personalized nutrition and FxMed.

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Medical Nutrition in Clinical Practice

BY NEDA GIOIA OD, CNS, FOWNS, CFMP

A paradigm shift that places nutrition and lifestyle as integral components of treatment plans alongside traditional medical interventions is a transition necessary for chronic disease management. Instead of solely focusing on managing symptoms or treating diseases reactively, this new model emphasizes the significant impact of nutrition and lifestyle on overall health and well-being. Health care providers, including doctors, nutritionists, and wellness coaches collaborate to create personalized treatment plans that not only address medical conditions but also prioritize preventive measures through education and empowerment and more recently AI technologies with real-time feedback. This is health care 3.0.

Adopting healthier eating habits, regular physical activity, stress management, and improved sleep patterns with evidence-based interventions are target points that most health care providers accept as important. Embracing a holistic model, health care systems can promote a culture of wellness, ultimately leading to improved patient outcomes, reduced health care costs, and a healthier population overall.

Governmental policies such as the National Institutes of Health Precision Nutrition Program are pioneering initiatives toward the growing field of precision nutrition. Holding promise in revolutionizing public health outcomes, the goal is to recognize the diverse and complex interactions between genetics, environment, and individual responses to diet. Researchers aim to decipher how molecular signatures interact with dietary patterns, ultimately shaping an individual's susceptibility to various diseases and their response to dietary interventions. These vital insights will help shape the future of nutritional science and inform evidence-based strategies to promote health, prevent disease, and optimize well-being on an individualized level. As this field continues to evolve, it holds great promise in revolutionizing public health paradigms and establishing a new era of precision medicine with nutrition at its core.[1, 2]

The foundation of creating an integrated approach is understanding and teaching the concept of modifiable risk factors. It is understood that these factors are under our control and can be altered through conscious efforts and proper support and guidance. Examples of modifiable risk factors include smoking, poor diet, physical inactivity, excessive alcohol consumption, and stress as mentioned by the World Health Organization. Health care professionals emphasize the importance of addressing these modifiable risk factors to promote preventive health measures and improve overall well-being.[3, 4]

As the field of optometry continues to evolve and diversify, incorporating services such as contact lenses, aesthetics, lasers, vision therapy programs, and low vision care, a pertinent question arises: How can we similarly integrate core nutritional aspects and lifestyle practices?

By exploring the implementation of functional nutrition within optometry, we can harness the potential benefits of utilizing dietary approaches with other important modifiable lifestyle changes such as movement, sleep, and stress reduction to enhance ocular health

and overall well-being. Integrating core nutritional principles into our practice requires a thoughtful approach involving education and infrastructure to effectively incorporate these essential components. Just as optometrists have embraced various innovative services, incorporating functional nutrition can further empower practitioners to provide comprehensive care that addresses both visual and systemic health improvement, which ultimately can bend the needle of improving our health care system.

Biomarkers Testing for Patient Compliance

By combining biomarker testing with clear communication and patient education, health care providers can enhance patient compliance and foster a collaborative approach to managing health conditions effectively. Tangible evidence of their condition and progress can motivate change.[5]

Testing biomarkers can play a significant role in improving patient compliance in several ways: (Table 1)

- **The results can be a motivating factor** for the patient, making them feel like an active participant.
- **The testing can help the practitioner personalize the protocol,** matching the patient's unique needs. This enhances their belief that the treatment plan is well suited for them individually.[6]
- **Biomarker testing can help detect health issues** at an early stage, even before symptoms manifest, allowing for timely interventions.[7]
- **Tracking progress over time can be easier to plan and execute.** Observing positive changes in biomarker levels or overall health status can reinforce the importance of adhering to the treatment plan.[8] Conversely, if the marker(s) don't improve, it may indicate the need for additional support.

Table 1.

BENEFITS OF BIOMARKER TESTING
Objective data can serve as motivation and reinforcement to patients.
Allows health care providers to create personalized treatment plans.
Helps detect health issues at an early stage, even before symptoms manifest.
Regular monitoring allows patients and health care providers to track progress over time.

Omega-3 Testing

As evidence-based studies support nutritional interventions, how can we start implementing this foundational care to our optometric population? Strategic biomarkers related to ocular dysfunction are a good start.

The incorporation of omega-3 supplementation has been widely employed in the management of ocular conditions, including dry eye syndrome, traumatic brain injury, and age-related macular degeneration, among others. A meticulous approach with a quantifiable blood test such as an omega index is in alignment with precision nutrition principles and can foster better therapeutic outcomes.[9]

Bioavailability and functional efficacy of omega-3 fatty acids are reduced by oxidative damage. The peroxidation of omega-3 fatty acids negatively impacts omega-3 status in humans.[10] As a result, the same dosage may not be effective in two different individuals. Therefore, analysis of the intracellular status would be a more precise indication of dosing requirements, especially in patients who may have comorbidities or other nutritional deficiencies.

Newer tools such as the direct-to-patient testing OmegaQuant streamline testing omega-3 status without the need for a complete CBC. As per the OmegaQuant website, "Omega-3 Index is the proportion of long-chain omega-3s, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), of all fatty acids in your red blood cell membranes. It reflects the omega-3 status of your body over the last four months." Other indices tested in the report can include Omega-6:3 ratio, AA:EPA ratio, and trans-fat index, with target reference ranges that can be utilized to help manage the patient's inflammatory state. In a clinical setting, even if a patient has already started taking omega-3 supplements, assessing their effectiveness can be done approximately three months later with dosing adjustments done accordingly to foster better compliance and results.[11, 12]

Just as optometrists have embraced various innovative services, incorporating functional nutrition can further empower practitioners.

Homocysteine as a Biomarker

Homocysteine, an amino acid, holds vital significance in diverse metabolic pathways within the body. It is produced during the metabolism of two essential amino acids, methionine and cysteine, which are commonly found in protein-rich foods such as meat, eggs, dairy products, and legumes.[13]

Hyperhomocysteinemia, characterized by elevated levels of homocysteine, has been associated with a heightened risk of various health conditions. These include cardiovascular diseases, neural tube defects, and neurodegenerative diseases. The rise in homocysteine contributes to the promotion of oxidative stress, endothelial dysfunction, and inflammation within the body, all of which exert detrimental effects on overall health.[14] In the eye, hyperhomocysteinemia has been linked to retinal vascular dysfunction, retinopathy, and even age-related macular degeneration. Elevated homocysteine can impair retinal blood flow, induce oxidative stress, and promote inflammation, contributing to retinal tissue damage.[15, 16]

Assessing the serum level of homocysteine (in addition to a standard CBC) is a valuable biomarker offering potential benefits in mitigating the risk of ocular disorders. As per LabCorp's norms, the average plasma homocysteine levels are expected to range from 0.0 to 14.5 umol/L in the adult population aged 18 to 60 years. Monitoring and maintaining homocysteine within this range could be a target for therapy in treating eye diseases.

The unfavorable effects of elevated homocysteine levels are influenced by multiple factors such as genetics, methylenetetrahydrofolate reductase (MTHFR) polymorphisms, dietary, and lifestyle choices. The modifiable risk factors, such as the consumption of folate, vitamin B6, and vitamin B12, can be adjusted to lessen the impact of hyperhomocysteinemia. This opportunity to reduce the adverse consequences linked to elevated homocysteine levels and promote better health outcomes is a biomarker that can be of high value.[17]

Methylenetetrahydrofolate Reductase (MTHFR) Polymorphisms

MTHFR polymorphisms play a significant role in influencing homocysteine levels. MTHFR is an enzyme vital for folate metabolism, crucial in DNA synthesis and methylation reactions within the body. Specifically, the MTHFR enzyme converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the primary circulating form of folate and an essential methyl donor involved in numerous cellular processes (CDC).[18] The MTHFR gene provides instructions for producing the MTHFR enzyme, which plays a critical role in the metabolism of folate. Genetic variations in the MTHFR gene, such as the C677T and A1298C polymorphisms lead to reduced MTHFR enzyme activity. The C677T variant is more common and has been associated with a more significant reduction in enzyme function compared to the A1298C variant. This reduced activity impairs the conversion of homocysteine to methionine, resulting in hyperhomocysteinemia.[17]

The mounting evidence highlighting the significance of hyperhomocysteinemia in the development of retinal diseases cannot be overlooked and can be deemed as a valuable tool for mitigating inflammation in the eye. Elsherbiny et al., indicate that inflammation induced by elevated homocysteine levels may contribute to dysfunction in the blood-retinal barrier and blood-brain barrier, thus contributing to the development of diabetic retinopathy, age-related macular degeneration, and Alzheimer's disease.[19]

Gopinath et al., demonstrated that elevated serum total homocysteine levels can serve as a potential indicator of an increased long-term risk of age-related macular degeneration. Older adults with deficiencies in vitamin B-12 and folate even face higher risk. Further research and validation in large cohort studies are essential, but we can start adopting a better dietary strategy incorporating folate-rich foods such as leafy green vegetables and appropriate fortified foods.[16]

In a hospital-based case-control study conducted by Satyanarayana et al., involving 300 patients with Type 2 diabetes and 100 control subjects, a significant correlation was identified between diabetic retinopathy and plasma hyperhomocysteinemia. The association was evident through elevated levels of homocysteine in the plasma of individuals with retinopathy highlighting

the potential role of hyperhomocysteinemia as a contributing factor to its development.[20]

From a therapeutic perspective, tackling elevated homocysteine levels involves identifying underlying factors such as dietary habits, lifestyle choices, and genetic variations that contribute to hyperhomocysteinemia. Effectively managing this condition requires implementing dietary modifications, supplementing with B vitamins (such as folate, vitamin B6, and vitamin B12), and considering other targeted interventions aimed at reducing homocysteine levels in the body.[21]

According to LabCorp reference B vitamin ranges are as follows:

- **Serum Vitamin B12 range:** 232 – 1245 pg/mL
- **Serum Folate (Folic Acid), range:** >3.0 ng/mL
- **Plasma Vitamin B6 range:** 3.4-65.2 ug/L

Objectively categorizing an individual's lifestyle needs based on biomarkers will unequivocally assist coordinating a more precision approach to nutrition and lifestyle recommendations.[22] ■

Dr. Neda Gioia, OD, CNS, FOWNS, is the founder and owner of Integrative Vision, an optometry practice in New Jersey with a distinct focus on nutritional interventions and functional medicine strategies for enhancing eye health. Her personal experience with nutrition inspired her to pursue a formal education in the field. Following her graduation from SUNY Optometry in 2006, she has earned functional medicine certifications and became a Certified Nutrition Specialist through the American Nutrition Association. She now serves as President of the Ocular Wellness and Nutrition Society. She also serves on the Women in Optometry board. Dr. Gioia is continuing her education path with the Institute for Functional Medicine and innovates with service-driven solutions such as her **SEEHealth** programs and **Eye Exam Plus.** Her enduring objective is to heal, educate, and empower both patients and fellow practitioners to integrate nutrition within health care practices in eye care.

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Research Update on Carotenoids and Brain Health

BY PROFESSOR JOHN M. NOLAN, PHD

Adding to the use of macular carotenoids for ocular health, recent research has demonstrated that carotenoids also play a key role in brain health and function. The many related research findings, which support a now biologically plausible rationale, are summarized as follows: Carotenoids and omega-3 fatty acids are localized in brain tissue. Retinal carotenoids (via the measurement of macular pigment) are related to brain carotenoid concentrations. Serum carotenoids and omega-3 fatty acids are related to brain concentrations of these compounds. Individuals with high serum and macular pigment carotenoids exhibit better cognitive performance compared to individuals with low serum and macular pigment carotenoids. Healthy individuals supplemented with carotenoids and omega-3 fatty acids exhibit improvements in cognitive function. Patients with Alzheimer's disease have lower levels of carotenoids compared to age-matched controls. Patients with mild cognitive impairment demonstrate improvements in global cognition following intervention with carotenoid and omega-3 fatty acids. Intervention with a combination of carotenoids and omega-3 fatty acids improves carotenoid levels and quality of life for patients with confirmed (mild/moderate) Alzheimer's disease. Here is the supporting research:

Professor John M. Nolan, PhD, is principal investigator, Nutrition Research Centre Ireland, South East Technological University.

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PHOTO CREDIT: David Malan/Getty Images

Personalized Nutrition Practitioner Training Program

ANA

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CERTIFIED PERSONALIZED NUTRITION PRACTITIONER℠

With nutrition taught in fewer than 20% of optometry and medical schools, it is up to each individual eye care professional to access their own education about ocular health and wellness. Fortunately, ECPs need look no further because the **Ocular Wellness & Nutrition Society** (OWNS) has partnered with the leader in personalized nutrition education, the **American Nutrition Association** (ANA).

ANA has developed a concise, clinically focused educational program to provide practitioners with the skills and knowledge to apply personalized nutrition to patient care. Practitioners who complete this program will receive a Certificate of Completion from the American Nutrition Association, earn 44 CME or CE credits, and meet coursework requirements to sit for the Certified Personalized Nutrition Practitioner (CPNP) exam and earn the CPNP credential.

The Time to Act Is Now

Right now, the National Institutes of Health (NIH) is in the middle of a decade-long strategic plan to advance nutrition research. Started in May 2020, the initiative's objective is for practitioners to be able to recommend what, when, why, and how everyone should eat to optimize their health, an approach known as "precision nutrition."

With the NIH continuing to strongly support research on eating patterns that promote wellness, the practitioner of the future will use food as medicine. The wellness movement is touching every segment of our society, and it's getting more sophisticated. Patients realize that their genes, lifestyle, and environment play a key role in their health, so the time for ECPs to specialize in this field is now.

OWNS: The Benefits of Membership

In support of this goal to educate ECPs to specialize in ocular health and wellness, OWNS has partnered with ANA and provides the following **benefits to its members:**

- **OWNS members receive a 35% discount** on the American Nutrition Association's **Personalized Nutrition Practitioner Training Program** (CPNP)
- **OWNS doctor lookup** for patients wanting a doctor with an interest in nutrition and wellness
- **Six hours of COPE-approved CE** annually featuring top doctors and scientists in the field
- **Monthly email and blog updates** on the latest in nutrition science
- **The opportunity to earn a fellowship** and receive the distinction of FOWNS
- **Free admission** to the in-person annual reception at the American Academy of Optometry
- **Free access** to American Board of Optometry (ABO) COPE-approved CE
- **Collaboration with the journal *Nutrients***
- **Various discounts** and promotions with affiliate industry companies

Personalized Nutrition for Brain Health

BY CORINNE BUSH, MS, CNS | DIRECTOR OF NUTRITION SCIENCE | AMERICAN NUTRITION ASSOCIATION

What Is Personalized Nutrition and How Does It Support Brain Health?

Personalized nutrition integrates deep assessment of your biochemistry, genomics and microbiome with your symptoms and input to understand your cognitive status. The first step is to test for the function of the Essential Elements of Brain Health.

1. Healthy Detoxification
2. Balanced Inflammation
3. Optimal Insulin Sensitivity
4. Healthy GI & Microbiome
5. Optimal Nutrient Status
6. Balanced Hormones

LAB TEST	ESSENTIAL ELEMENT INDICATOR
C-Reactive Protein	Balanced Inflammation
Fasting Insulin	Optimal Insulin Sensitivity
Hemoglobin A1C (HgA1C)	Optimal Insulin Sensitivity; Balanced Inflammation
Homocysteine	Balanced Inflammation; Optimal Nutrient Status
25 Hydroxy Vitamin D	Balanced Inflammation; Optimal Nutrient Status; Healthy Detoxification
Vitamin B12	Nutrient Status; Healthy GI and Microbiome
Zinc:Copper Ratio	Balanced Inflammation; Nutrient Status; Detoxification
Glutathione	Nutrient Status; Healthy Detoxification
Cortisol & Sex Hormones	Balanced Hormones; Balanced Inflammation
Thyroid Hormone Panel	Balanced Hormones

10 Important Tests for Brain Health: Work with your personalized nutrition practitioner and your physician to order and interpret lab test results.

A balanced brain is the result of fine-tuning these elements to support healthy function by preventing and reversing damage that leads to mood and cognitive dysfunction.

What Should I Do When I Get My Lab Results Back?

Work with a practitioner who can translate your lab results and matrix them with your symptoms and feedback to give you a sense of your overall brain health. Your practitioner can then create an individualized plan to address imbalances, address symptoms and improve brain health.

Even without extensive testing, there are a few things that everyone can do to support brain health today!

1. Include a variety of organic and colorful plantfoods such as vegetables, fruits, nuts, seeds, legumes, herbs and spices which contain many essential nutrients such as B vitamins, magnesium, zinc, plant flavonoids, and anti-inflammatory compounds.

2. Replace refined carbohydrates such as sweets, breads, and pastas with whole grains and prebiotic fibers from root vegetables, dark leafy greens and onion-family foods.

3. Increase intake of foods that contain both omega-3 fatty acids and choline such as wild Alaskan salmon, farm fresh eggs, and flaxseeds.

4. Use healthy oils and fats that promote intestinal, microbial, heart, and brain function such as organic ghee from grass-fed cows, olive oil, and coconut oil.

5. Choose high-quality proteins such as wild fatty fish, organic poultry, farm fresh eggs, and grass-fed/grass-finished meat and dairy.

6. Replace sugary beverages and alcohol with plenty of water and unsweetened tea.

7. Start your day off right with lower-carb options such as eggs and sauteed vegetables, a green smoothie, or full fat organic yogurt with berries, nuts, and seeds.

8. Practice intermittent fasting by allowing 12-14 hours to pass without eating or drinking caloric beverages between dinner and the next day's breakfast.

9. Encourage BDNF production in the brain. Reduce carbohydrates and increase omega-3 fats, curcumin, sleep, meditation, and stress reduction.

10. Take high quality supplements as recommended by your health care team to bring the Essential Elements of Brain Health back into balance. ■

Corinne Bush, MS, CNS, is co-owner of Lotus Nutrition, a nationwide team of Personalized Nutrition professionals who serve the New York and San Diego metropolitan areas.

Tribute to Dr. Stuart Richer

BY DENNIS RUSKIN, OD, FAAO

In the vast tapestry of the eye care and scientific community, few luminaries shine as brightly as Dr. Stuart Richer. His untimely passing leaves behind a legacy of passion, dedication, and visionary thinking that transformed the world of optometry and vision science. Recognized by many as the father of carotenoid nutrition research in North America, Dr. Richer's groundbreaking contributions have fundamentally shaped our understanding of the vital links between nutrition and ocular health.

Dr. Richer was not just a man of science but also a man of immense passion and dedication. His intense commitment to the care of our nation's veterans, and the pioneering science of vision loss prevention, stands as a testament to his unwavering work ethic and dedication to his craft. His work was fueled by innovative thinking, often introducing methods and insights that were ahead of their time, challenging and expanding the boundaries of conventional wisdom.

His scientific contributions are vast and varied. Dr. Richer presented research papers and participated in symposiums at the American Academy of Optometry, the Association for Research in Vision Ophthalmology, and key global international conferences. Dr. Richer held the esteemed position of president of the Ocular Wellness and Nutrition Society. He served as the associate editor of the *Journal of the American College of Nutrition,* and he was an associate professor of family and preventative medicine at Chicago

PUBLICATION DATE	TITLE OF CLINICAL STUDY OR DISCOVERY
1977	Increasing Visual Detectability in Reduced Exposure Mammography by Contrast Adjustment" (1977). Stuart Richer's thesis for his PhD[1]
1998	Ocular Oxidants and Antioxidant Protection[2]
1998	Water soluble antioxidants in mammalian aqueous humor: interaction with UVB and hydrogen peroxide
2004	Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study
2007, 2010	Differential temporal responses of macular pigment optical density in patients with atrophic age-related macular degeneration to dietary supplementation with xanthophylls
2011	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)
2013	Observation of human retinal remodeling in octogenarians with a resveratrol based nutritional supplement
2014	Resveratrol Based Oral Nutritional Supplement Produces Long-Term Beneficial Effects on Structure and Visual Function in Human Patients
2017	Improved Visual Acuity and Retinal Integrity with Resveratrol Based Supplementation in Patients with Macular Degeneration
2017	Longevinex®observed to improve AMD Clinical Dark Adaptation[11]
2017	Longevinex ® Improves Human Atrophic Aged-related Macular Degeneration (AMD) Photoreceptor / Retinal Pigment Epithelium Mediated Dark Adaptation
2017	Restoration of Central Macular Pigment Dip with Dietary RR Zeaxanthin Supplementation in Patients with AMD
2018	Of Vanishing Retinal Drusen and Oxysterols[15]
2018	Statins, Caloric Restriction and Longevinex® in a One-eyed Patient with Macular Drusen[16]
2021	A Randomized Placebo Controlled Clinical Trial on Effects of Carotenoid Supplementation on Night Vision in Older Adults
2021	Night Vision and Carotenoids (NVC): A Randomized Placebo Controlled Clinical Trial on Effects of Carotenoid Supplementation on Night Vision in Older Adults. Nutrients
2022	Reply to Green-Gomez et al. Comment on "Richer et al. Night Vision and Carotenoids (NVC): A Randomized Placebo Controlled Clinical Trial on Effects of Carotenoid Supplementation on Night Vision in Older Adults. Nutrients

Stuart Paul Richer, OD, PhD, FAAO

Medical School. Furthermore, he was the global scientific director of the Zeaxanthin Trade Association. Dr. Richer also provided valuable consultancy to many organizations dealing with nutrition and device interventions.

Beyond his impressive clinical research, Dr. Richer displayed a deep sense of empathy and compassion. He consistently prioritized the education of his patients and the wider public, ensuring they had the knowledge to make informed decisions about their health. This selflessness and care were evident in his leadership in OWNS, a group dedicated to teaching doctors and patients about improved quality of life and vision loss prevention.

His charisma and influential nature were undeniable. Dr. Richer's annual publication—a prevention and wellness guide for eye doctors—became an eagerly awaited resource, distributed to over 40,000 eye doctors internationally. His ability to inspire, to rally others behind his vision, showcased his innate leadership qualities.

Yet, what makes Dr. Richer's legacy even more remarkable is his integrity. He held strong convictions about the potential links between nutrition, lifestyle, and ocular wellness, and he pursued these avenues with an unwavering commitment to scientific rigor and truth.

Some of Dr. Stuart Richer's significant discoveries and contributions to mankind are listed in the chart opposite.

I was fortunate to have met and known Stu. We have lost not only a brilliant scientist but also a dear friend who touched our lives in countless ways. Stu was the embodiment of many virtues: a genuinely kind-hearted individual, deeply religious, a devoted family man, and a beacon of inspiration for patients, students, and colleagues alike. In his passing, the world has lost a luminary, but his spirit and legacy will continue to inspire and guide us. As we remember Stu, let us cherish the moments shared, the knowledge imparted, and the lives he enriched. ■

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