

Evidence Supports New Approaches for Reducing the Risk of Macular Degeneration

Learn about the pathogenesis of MD, how to identify patients at risk and slow its progression through diet and nutritional supplementation.



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Advances in science and modern medicine have increased life expectancy. Living longer, however, implies nothing about the quality of life. The aging of the baby-boomer generation coincides with an expected epidemic rise in vision impairment caused by age-related macular degeneration (AMD). Current estimates report that 30 million people worldwide have AMD, and the number is expected to double or triple in the next 20 years. The associated costs are astronomical. As gatekeepers for vision care, eyecare practitioners can play an important role in preventing vision impairment from AMD and reducing healthcare costs by proactively screening their patients for risk and taking appropriate measures to reduce that risk.

Prevention represents a paradigm shift from the traditional model of “sick” health care. This is of particular importance because the public is relatively unaware of what AMD is, and that it’s 2.5 to 3.5 times more prevalent than glaucoma.

An important component of this paradigm shift is the elimination of the words “age-related” from age-related macular degeneration. AMD is a misnomer (hereafter referred to as MD). Although the disease may present itself late in life, current thinking suggests that ocular changes begin decades before the onset of signs or symptoms.

The words “age-related” imply that younger people don’t need to be concerned about the disease, creating a false sense of security. This false sense of security hinders the ability of eyecare practitioners to drive home the concept

of screening, detecting, intervening and preventing.

The MD Patient

Clinicians don’t see the problem of MD the way patients do. We look into their eyes, but they must look out of them. It’s easy to become jaded when the involvement is through peripheral experience. For the MD patient, life is altered far beyond the examination room evaluation. Visually, aside from the loss of central visual acuity, patients experience a loss of contrast sensitivity, color vision, depth perception, glare recovery, facial recognition as well as reading and driving ability. Practitioners need to be more sensitive to the emotional toll that vision loss takes on the lives of their patients. MD patients experience a sense of loneliness, isolation, helplessness, depression and a loss of independence. It can be a devastating experience. Understanding all of the disease’s ramifications will propel every eyecare professional to the highest level of commitment in a common effort to prevent the continued rise in MD cases.

Theories of MD Pathogenesis

Although the exact mechanism of MD has yet to be determined, two very strong theories for its pathogenesis have come to the forefront: oxidative stress from cumulative blue light damage and reactive oxygen species (ROS) damage.

An evolutionary theory of MD is worthy of mention. Because the basis for evolution is reproduction, once we’re beyond the reproductive years, dormant

genes could become active. These genes could set in motion the aging processes that lead to MD by promoting light-induced oxidative stress and ROS damage.

The macula is a unique and miraculous structure. It’s arguably the most at-risk part of the human body. Not only is it sensitive to light stimulation, but the light that reaches it is focused to a high intensity. The eye is particularly vulnerable to blue light damage, also known as high energy visible light (HEV). HEV encompasses light from 400 nm to 500 nm.¹ The abiotic effects of HEV-induced damage are permanent and cumulative over a lifetime. The delicate macular tissue is also among the most active of tissues in our body, which necessitates a high rate of cellular metabolism. Supporting this high rate of metabolism is the critically located blood-rich choriocapillaris and, to a lesser extent, the perimacular retinal arcades and a central artery (present in 25% of eyes). The byproduct of an accelerated rate of metabolism is the production of a large number of ROS.

ROS and Free Radicals

ROS encompass all of the unstable molecules produced as a result of HEV photochemical reactions, as well as normal cellular metabolism for the creation of cellular energy, including retinal pigment epithelium (RPE) phagocytosis and the photosensitizers. The high oxygen level present in the macula, coupled with its high metabolic rate, creates an extreme number of ROS that need to be quenched. An ROS subcategory, called



free radicals, consists of atoms or molecules high in energy and in need of electrons, such as superoxide, nitric oxide and the hydroxyl ion.² Free radicals aren't too particular about where they take the electrons from, and damage to molecules needed for proper cellular structure and metabolic processes results.

ROS also encompass other atoms or molecules, such as singlet oxygen, hydrogen peroxide and hypochlorous acid, which even with a full complement of electrons are unstable. In the macula, the production of an excess of ROS, beyond the quenching capability of the existing antioxidants, leads to photoreceptor phospholipid (polyunsaturated fatty acids or "PUFAs") oxidation (an easy source for electrons) and damage. This phospholipid oxidation leads to the formation of lipofuscin, which when accumulated, is commonly known as drusen. The oxidized phospholipid, now in need of an electron, continues a cascade of electron stealing.² Lipofuscin is an aggregate of nondegradable oxidized lipids (known as A2E) and protein particles. Recently, oxidative damage also has been implicated as an inducer of an inflammatory response that can hasten the entire process.³

Antioxidants

The predominant antioxidants available to the retina include vitamins A, C and E, and the three macular carotenoids lutein, zeaxanthin and meso-zeaxanthin. Collectively, lutein, zeaxanthin and meso-zeaxanthin make up the macular protective pigment (MPP). Zinc is present in the macular tissue, but it facilitates the process of eliminating the ROS and isn't an actual antioxidant.

A recently published study⁴ describes a breakthrough discovery as to how antioxidants protect the photoreceptors and other retinal cells. The study shows how A2E, which doesn't break down, can build up in the cells. The creation of A2E, a component of lipofuscin, is a natural byproduct of cellular metabolism. In the presence of

HEV-induced oxidative stress, A2E disrupts the normal functioning of mitochondria, and cells die. A cell can't sustain viability without adequate energy production. The study showed that antioxidants could counter the damage. This appears to be evidence-based validation of the protective role of MPP.

wise, HEV at low levels, with extended duration, can cause photochemical damage. It doesn't take many of these very high-energy short-wavelength photons to produce permanent biological damage over time.⁸ HEV, outside of blue, isn't known for causing significant rises in temperature. Studies have

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The European Eye Study⁵ similarly concluded that exposure to blue light and a low serum level of antioxidants is associated with the development of MD.

Other evidence recently has surfaced concerning the protective role of carotenoids. In a randomized, placebo-controlled, double-blind study⁶ on the effects of oral lutein and zeaxanthin on skin, a mechanism of action for carotenoids has been clearly demonstrated. Women given 10 mg/day versus placebo were found to have four significant beneficial changes. They experienced measurable increases in skin hydration, elasticity and lipid content and a decrease in skin lipid peroxidation. The decrease in lipid peroxidation would appear to be the same mechanism and benefit that MPP carotenoids produce in the macula.

High-Energy Visible Light Hazard

Exposure to blue light can accelerate aging of the eye because the damage threshold for the RPE is lowest for blue light.⁷ The primary mechanisms for blue light damage are thermal and high energy (actinic). Absorption of blue light in the RPE and choroid can cause an increase in temperature sufficient to cause thermal damage. Like-

shown that blue light can cause macular hypopigmentation, as seen in MD. The potential for damage is increased for individuals who spend a significant amount of time outdoors, don't wear appropriate solar-blocking eyeglasses and don't wear hats. Consideration must be given for indirect and scattered blue light exposure. This applies even more for children, who spend a great deal of time outdoors and whose ocular pigmentation hasn't achieved adult protective levels.

Risk Factors

Many risk factors have been associated with the development of MD. There have been some conflicting studies, but the general consensus classifies them as follows:

1. Nonmodifiable risk factors.

Age, family history/genetics, female gender, light iris color/pigmentation hyperopia and diabetes.

2. Modifiable risk factors.

Carotenoid/dietary deficiency, smoking, obesity, lifetime sun exposure, cardiovascular disease, diet lacking in antioxidants, elevated serum lipids, alcohol consumption and a sedentary lifestyle.

A common thread runs through most of these risk factors: a decrease in

serum carotenoid and antioxidant levels, or a decrease in blood perfusion through the perifoveal retinal arcades and/or choroidal capillaries, which would have the same effect. Age has its own associated decrease in carotenoid levels and blood flow. Smoking is thought to increase the risk for MD by decreasing blood flow, oxygen and serum carotenoid levels and the level of antioxidants while increasing ROS.⁹ Likewise, excessive alcohol consumption decreases serum carotenoid and antioxidant levels.¹⁰

Dealing With HEV, Free Radicals

The human eye at birth is void of the protective pigment layer, consisting of carotenoids that deal with HEV and ROS. The introduction to carotenoids comes from a mother's milk. Humans don't possess the ability to manufacture them. Out of the more than 600 carotenoids that exist in nature, only three are found in the macula: lutein, zeaxanthin and meso-zeaxanthin. These three carotenoids make up the MPP, which is the yellow layer known as the macula lutea (yellow spot).

Carotenoids must be consumed to enter the blood stream and be actively transported to, and accumulated in, the center of the macula. High performance liquid chromatography (HPLC), a chemical analysis that separates and measures individual molecule quantities, performed on tissue from autopsy eyes has shown the presence of lutein, zeaxanthin and meso-zeaxanthin. Serum analysis, however, only shows the presence of lutein and zeaxanthin, leaving the source of meso-zeaxanthin a mystery. In one study involving carotenoid-deprived monkeys, one group had only lutein introduced to the diet, while another group had only zeaxanthin introduced. Post mortem evaluation showed that those given lutein had both lutein and meso-zeaxanthin in their macula, while those given zeaxanthin had only zeaxanthin.¹¹ This indicates that meso-zeaxanthin is created in the center of the macula from lutein. The exact mechanism of conversion has not yet been de-

termined, but speculation is high that the process is enzyme-mediated.¹² Carotenoids have been shown to be safe and nonmutagenic.

Powerhouse Carotenoids

Researchers have long been aware of the existence of lutein, zeaxanthin and meso-zeaxanthin, but the bulk of information, published in chemical and research journals, has only recently become more widely available. Many new research projects are on the horizon and are expected to lead to an explosion of new articles. MPP has been linked to a decreased risk of heart disease and cancer and the prevention or slowing of cataract development. Carotenoids are water insoluble and transported by lipoproteins.¹³ Therefore, they need fat to be absorbed. High-density lipoprotein (HDL) is the good cholesterol that's elevated as a result of statin drug therapy. HDL is thought to be the main lipoprotein vehicle for transporting lutein in serum. The possibility of statin intervention and carotenoid supplementation synergy is an intriguing area of ongoing research.

Critical Location of MPP

MPP resides in the Henle photoreceptor axon layer and the inner and outer plexiform layers of the macula and is bound there by the common structural protein tubulin.¹⁴ The optically dense MPP is ideally situated to protect the macular tissue. This critical location places it anterior to and independent of the melanin-rich RPE (**Figure 1**). The MPP is likened to a "shield" protecting the tissue below. The macular carotenoids are architecturally positioned for maximal antioxidant and light filtration activity. In addition to cellular

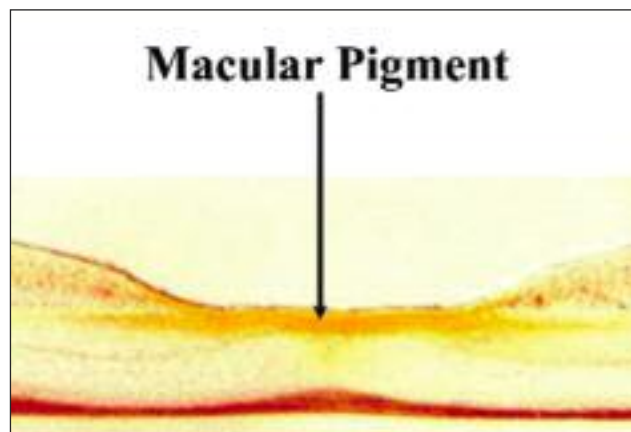


Figure 1. The optically dense macular protective pigment (MPP) is located anterior to and independent of the melanin-rich retinal pigment epithelium, making it ideally situated to protect macular tissue below.

protection, the MPP is thought to enhance vision by decreasing chromatic aberration and removing atmospheric blue haze. The macula is the only place in the human body where the carotenoids lutein and zeaxanthin accumulate at a concentration 10,000 times that found in blood. Amazingly, it's the only site in the human body where meso-zeaxanthin exists.¹⁵

Macular Carotenoid Distribution

Across the macula, MPP distribution takes the form of a mountain, peaking centrally at the foveola and declining to nil at an eccentricity of 7°. Meso-zeaxanthin concentration is greatest at the peak of the mountain (**Figure 2**) and decreases rapidly away from the peak. The concentrations of lutein and zeaxanthin are higher at the lower elevations and decrease to nil as they approach ground level, at 7° eccentricity. The favorable positioning of meso-zeaxanthin is discussed below.

Properties of Meso-zeaxanthin

Meso-zeaxanthin resides directly over the center of the macula, where light is focused and where the strongest need for hazardous actinic blue light protection exists. It's the strongest antioxidant of the three, and it allows for a wider range of blue light filtration. In nature, meso-zeaxanthin has been isolated in shrimp, certain turtles and yellow fish

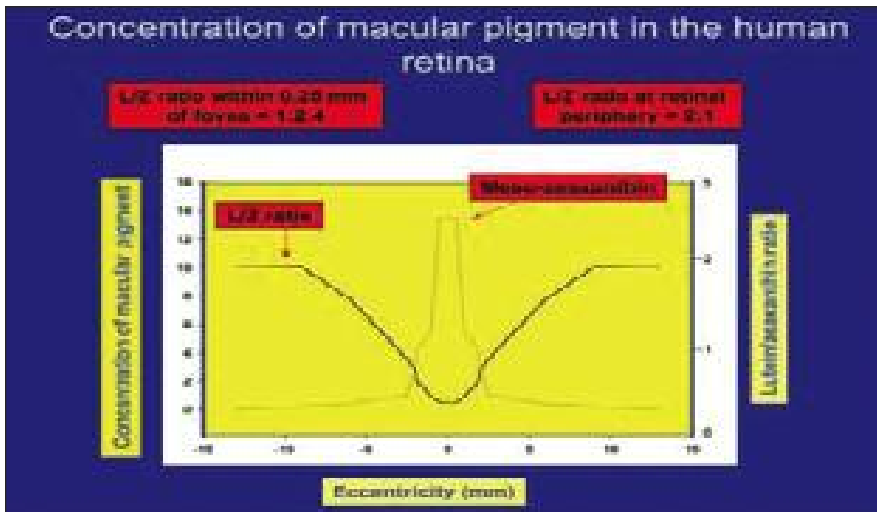


Figure 2. Across the macula, MPP distribution takes the form of a mountain, peaking centrally at the foveola and declining to nil at an eccentricity of 7°.

skin.¹⁶ Although not normally a part of our diet and undetectable in blood serum, meso-zeaxanthin is of such importance to the eye that it's exclusively manufactured there. As a result of meso-zeaxanthin supplementation, increased macular protective pigment density (MPPD) has shown the carotenoid to be actively transported to and accumulated in the macula.¹⁷

An MPP deficiency can result from an insufficiency in dietary carotenoids, an inability to absorb them or a lack of ability to convert lutein into meso-zeaxanthin. The inability to create meso-zeaxanthin is a theory that is gaining in popularity. Using a densitometer, which measures carotenoid levels at varying degrees of eccentricity, a dip was discovered in some patients at the MPP mountain top, where meso-zeaxanthin should be located. Further research involving a randomized, double-blind, placebo-controlled study will soon be conducted at the Waterford Institute of Technology, Macular Pigment Research Group, in Waterford, Ireland. This study should give credence to or debunk this theory.

Measurement Instruments

Currently, two devices are available for measuring low MPPD, one of the primary risk factors for MD: the

MacuScope (MacuChek, West Bloomfield, Mich.) and QuantifEYE (ZeaVision, Chesterfield, Mo.). The MacuScope has been validated as a true heterochromatic flicker photometry (HFP) device. Its accuracy has been matched to other research instruments, such as Raman spectrometers, scanning laser ophthalmoscopes and densitometers, which have been shown to be too expensive and cumbersome for practical use.

Attributes of HFP

HFP utilizes two alternating light sources: a blue light at a wavelength of 460 nm and a green light with a 540-nm wavelength. The blue wavelength is absorbed solely by the MPP, present only in the central macula, while the absorption of the green wavelength is unaffected by the MPP.¹⁸

To determine the amount of blue 460-nm light absorbed by the MPP, testing is split into two threshold measurements that must be taken. One is through the center of the fovea where

the highest concentration of MPP is found. The second is at an eccentricity of 8° where the MPP doesn't exist (Figure 3). It's critical that the second reference point be determined to accurately measure MPPD. Without this control measurement taken and subtracted, only an estimated MPPD will result.

When the alternating blue/green stimuli is viewed, green isn't perceived. The colors are fused into a blue pulsating light. For each part of the test, a circular neutral density filter is rotated in calculated steps of increasing density, or decreased light transmission for the blue stimulus. This is done until the patient identifies the null point or minimum level of pulsation. The null point occurs when the brightness (luminance) of the blue 460-nm stimulus matches the brightness of the green 540-nm stimulus. The difference in luminance between the two measurements has a logarithmic relationship to the MPPD, which is calculated and quantified in units of absorption. Remember that the MPP filters out and removes some of the blue 460-nm light; therefore, more blue light is required for the fovea measurement than for the parafovea

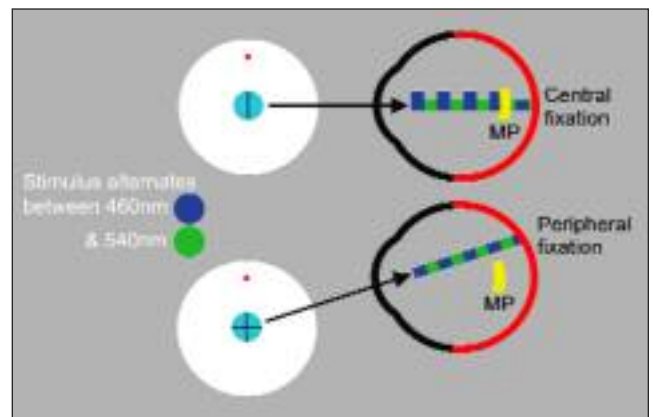


Figure 3. The MacuScope, using heterochromatic flicker photometry, takes two measurements. One is through the center of the fovea where the highest concentration of macular protective pigment (MPP) is found. The other, a reference point, is at an eccentricity of 8° where the MPP is nil.

measurement.¹⁸ Only one eye needs to be tested, because no statistically significant difference between the two has been found, even though one eye may develop MD earlier.

The resulting printout contains the two measurements, the calculated difference (MPPD), and an automatically calculated grading based on a normative database. The scale for the normative database also is printed out. The eye-care practitioner determines the need for interventional supplementation therapy based on MPPD and other risk factors for MD the patient may have.

Taking a psychophysical (subjective) test requires a patient who can understand the instructions, fixate steadily and make a fine discrimination. The test requires a visual acuity of 20/40 or better, can accommodate +6.00D to -6.00D uncorrected refractive error, or can be done with contact lenses or eyeglasses. HFP has been proven to be accurate and repeatable. In addition, clinicians can use the MacuScope to detect acquired MPP loss over time and monitor the impact of therapeutic intervention.

Effective Supplementation

For patients with a low MPPD or a low average MPPD coupled with other risk factors, practitioners can prescribe an oral supplement that contains all three carotenoids. Currently,

MacuHealth with LMZ³ is the only available triple carotenoid supplement (Table 1). It contains lutein-10 mg, meso-zeaxanthin-10 mg and zeaxanthin-2 mg (proprietary formula). It doesn't contain the AREDS formula, which is only indicated for patients with significant drusen. In addition, it doesn't contain any of the long list of ingredients (up to 45) found in many designer-type supplements. Patients need to take just one LMZ³ capsule per day, not multiple capsules multiple times, which fosters compliance. Because carotenoids are absorbed through fat intake, patients should take the capsule with the fattiest meal. LMZ³ has no known drug interactions, side effects or contraindications. Patients get excited that the effects of supplementation can be measured, which results in family referrals.

Studies have shown that increases in MPPD can be measured in 6 months, at which time the patient should have their MPPD rechecked.¹⁹ Most patients will plateau at approximately 2 years. At that time, clinicians should give consideration to cutting back from daily to every other day, and check the patient periodically for an MPPD decline.

AREDS Report 22²⁰ focused on the 4,600 participants from the original AREDS study. Each of the participants had one of the four stages of MD. The researchers gathered extensive dietary information and evaluated dietary consumption of vitamins A, C, E and carotenoids to determine if any correlation existed between their intake and progression of MD. The conclusion was that only the dietary intake of carotenoids correlated with a decreased rate of progression for any of the four stages of MD. This makes a very compelling case for placing every patient at any stage of MD on a triple carotenoid supplement. Unfortunately, the AREDS 2 study (due for completion in about 5 years), which is evaluating the possible benefits of lutein and zeaxanthin and omega-3 fatty acids in combating MD progression, doesn't include meso-zeaxanthin.

The average Western diet contains fewer than 3 mg of lutein and zeaxanthin daily.²¹ Approximately 20 mg of carotenoids per day are needed to effectively repigment the macula. That translates to about a bucket of green leafy vegetables per day. It would be very difficult, or next to impossible, to raise MPPD through diet alone.

In studies to date, once the macula is repigmented, some patients have experienced improvements in their visual acuity, contrast sensitivity, color appreciation and glare recovery time.²² Patients who have had photo-documented macular drusen and low MPPD have been treated with LMZ³. Their MPPD significantly increased, and subsequent retinal photographs showed a disappearance of central drusen (Figure 4 and Figure 5). More cases are being collected.

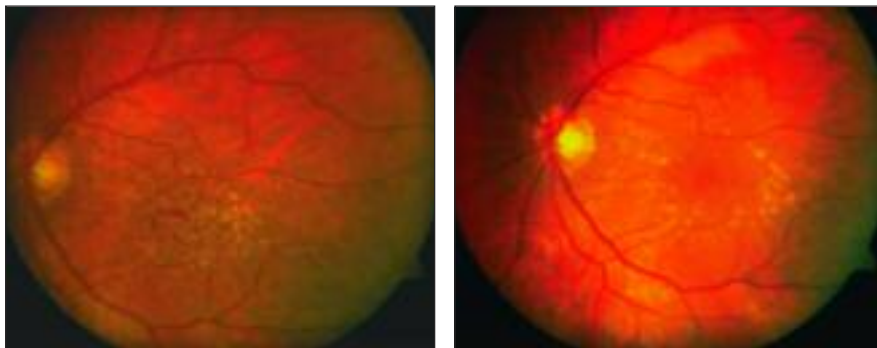
Science Supports Nutrition

The old mantra of eating well to stay healthy is finding new and convincing support. The eye is under constant assault from blue light, ROS, medications, pesticides, genetics, ozone, pollution, alcohol and tobacco. This is by no means an exhaustive list. Aside from sunglasses and hats, diet and nutrition

Supplement Breakdown by Macular Protective Pigments Based on Single Tablet/Capsule

	Lutein	Zeaxanthin	Meso-Zeaxanthin	Total MPP Carotenoids
MacuHealth with LMZ ³	10 mg	2 mg	10 mg	22 mg
Zeavision – EyePromise Restore	4 mg	8 mg	0 mg	12 mg
Zeavision – EyePromise Ten	10 mg	0 mg	0 mg	10 mg
Bausch & Lomb – Ocuvite/Lutein	6 mg	0 mg	0 mg	6 mg
Bausch & Lomb – PreserVision	5 mg	0 mg	0 mg	5 mg
Alcon – ICaps AREDS	0 mg	0 mg	0 mg	0 mg
Alcon – ICaps Lutein/Zeaxanthin	2 mg	2 mg	0 mg	4 mg
Alcon – ICaps Lutein/Zea/Omega3	3 mg	3 mg	0 mg	6 mg
AmeriScience – TOZAL	10 mg	0.5 mg	0 mg	10.5 mg
Wyeth – Centrum Silver	.25 mg	0 mg	0 mg	.25 mg
Lange Eyecare & Associates – Fortifeye Complete	10 mg	10 mg	0 mg	20 mg

Table 1. MacuHealth with LMZ³ is the only available triple carotenoid supplement. It contains lutein, zeaxanthin and meso-zeaxanthin and has no known drug interactions, side effects or contraindications.



Figures 4 and 5. In some patients treated with a triple carotenoid supplement, macular protective pigment density (MPPD) has increased and central drusen have disappeared.

appear to be the best strategy for preserving and maintaining good vision for a lifetime. Along with some key nutrients, it's the antioxidants and the dual role of the carotenoids serving as both antioxidants and blue light filters, that appear to be the key protectors of healthy vision.

A broad spectrum of antioxidants has been indicated as protective of the macula. They include vitamins A, C and E, alpha-carotene and beta-carotene, L-glutathione and beta-cryptoxanthin. Other nutrients linked to playing a key

role in macular health are zinc, copper and selenium. Microvascular blood flow increase has been associated with ginkgo biloba and bilberry extract. Polyphenols and the long-chain omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) exhibit anti-inflammatory and macular protective qualities.

Most likely, the dual action of the dietary carotenoids lutein, zeaxanthin and meso-zeaxanthin represent the 1–2 combination punch for protecting the macula.

Looking Ahead

Eyecare practitioners should take a more proactive role in educating patients about the lifestyle choices that can put their vision at risk. This conversation should go beyond sports, sun exposure and occupational needs. Lifestyle issues such as diet and nutrition, smoking and obesity must be addressed.

Ongoing research, in the United States and abroad, likely will determine in the near future that multiple definitive links exist to further tie MPP supplementation and macular repigmentation to protecting the macula from MD development and progression. Preventive care via risk assessment, coupled with effective early intervention, may end the battle against MD that leads to permanent vision loss. **OM**

Dr. Snider is in private group practice in Bloomfield Twp., Mich. He's a consultant for MacuChek and has a minority interest in MacuHealth, LLC. Dr. Snider has written and lectured on macular degeneration prevention, screening and supplementation.

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- The high oxygen level present in the macula, coupled with its high metabolic rate, creates an extreme number of which of the following that need to be quenched?**
 - Phagocytes
 - Atoms
 - Electrons
 - Reactive oxygen species (ROS)
- Which of the following is present in the macular tissue but facilitates the process of eliminating the reactive oxygen species (ROS) and isn't an actual antioxidant?**
 - Zinc
 - Vitamin A
 - Vitamin C
 - Vitamin E
- According to a recent study, A2E, a component of lipofuscin and a natural byproduct of cellular metabolism that doesn't break down, does what in the presence of high energy visible light (HEV)-induced oxidative stress?**
 - Disrupts the normal functioning of mitochondria
 - Damages cell membranes
 - Produces cytotoxicity
 - Causes faulty DNA replication
- Absorption of blue light in what parts of the eye can cause an increase in temperature sufficient to cause thermal damage?**
 - Choriocapillaris and ciliary body
 - Retinal pigment epithelium and choroid
 - Optic nerve
 - Perifoveal retinal arcades
- Which of the following is *not* a modifiable risk factor for macular degeneration (MD)?**
 - Carotenoid/dietary deficiency
 - Smoking
 - Obesity
 - Diabetes
- Smoking is thought to increase the risk for MD by decreasing blood flow, oxygen and serum carotenoid levels and decreasing the level of which of the following?**
 - ROS
 - Zinc levels
 - Antioxidants
 - Vitamin D
- Out of the more than 600 carotenoids that exist in nature, how many are found in the macula?**
 - 3
 - 4
 - 5
 - 6
- Meso-zeaxanthin is likely created in the center of the macula from which of the following?**
 - Vitamin C
 - Vitamin A
 - Lutein
 - Zeaxanthin
- Macular protective pigment (MPP) has been linked to a decreased risk of heart disease and cancer and the prevention or slowing of which of the following conditions?**
 - Glaucoma
 - Diabetic retinopathy
 - Diabetic macular edema
 - Cataracts
- What is the main lipoprotein vehicle for transporting lutein in serum?**
 - High-density lipoprotein (HDL)
 - Low-density lipoprotein (LDL)
 - Triglycerides
 - None of the above
- Although not normally a part of our diet and undetectable in blood serum, which carotenoid is of such importance to the eye that it's exclusively manufactured there?**
 - Zeaxanthin
 - Lutein
 - Meso-zeaxanthin
 - Cryptoxanthin
- Heterochromatic flicker photometry requires a visual acuity of which of the following?**
 - 20/30 or better
 - 20/40 or better
 - 20/50 or better
 - 20/60 or better
- Patients with a low MPPD or a low average MPPD should take an LMZ³ capsule with which of the following?**
 - The fattiest meal
 - A low-fat meal
 - Low-fat milk
 - Orange juice
- Approximately how many milligrams of carotenoids per day are needed to effectively repigment the macula?**
 - 10 milligrams
 - 20 milligrams
 - 30 milligrams
 - 40 milligrams
- Which nutrient has not been indicated as protective of the macula?**
 - Vitamin A
 - Vitamin C
 - Ginseng
 - Selenium