

## Macular Degeneration (Age-related)

### OVERVIEW

Age-related macular degeneration (AMD) is a condition characterized by the deterioration of the macula portion of the eye. Macular is derived from the Latin word *macula*, meaning “spot.” The macula is the central and most vital area of the retina, providing the clearest, most distinct vision needed in reading, driving, seeing fine detail, and recognizing facial features, for example. There are two forms of macular degeneration: atrophic (dry) and neovascular (wet). Both forms of the disease may affect both eyes simultaneously. Vision can become severely impaired, with central vision rather than peripheral vision affected. The ability to see color is generally not affected, and total blindness from the condition is rare.

### EPIDEMIOLOGY AND GENETICS

#### Prevalence

AMD is the leading cause of irreversible visual impairment and blindness among Americans 65 and older. More Americans are affected by AMD than are affected by cataracts and glaucoma combined. Approximately 85–90% of the cases of AMD are the dry type. Although atrophic AMD accounts for most diagnosed cases, neovascular AMD is responsible for nearly 80–90% of significant visual disability associated with the disease.<sup>1</sup> The average age of onset of visual loss is 75 years, but after the age of 50 the incidence steadily increases, with more than one third of people over the age of 90 affected.<sup>2</sup> The eye-health organization Prevent Blindness America estimates that 13 million Americans have evidence of macular degeneration, while the Macular Degeneration Partnership places the number at closer to 15 million. It is equally common in men and women, with a higher incidence in whites than in blacks, and has a heritable nature.<sup>3,4</sup>

#### Symptoms and Disease Progression

The atrophic (dry) type of macular degeneration progresses more slowly than the neovascular (wet) type, with vision lost painlessly. In atrophic AMD, a thinning of the macula may initially produce blurry vision or distortion; more advanced cases will result in blank spots in the central visual field as the macula degenerates. Decreased reading ability, especially in dim light, and difficulty in adapting to dim light and the dark are common symptoms.<sup>5</sup> A vision test sometimes reveals physical deterioration before symptoms occur. Early detection of atrophic AMD is important to stave off the more debilitating neovascular AMD.<sup>6</sup>

In neovascular AMD, blood vessels below the retina undergo abnormal growth into the retina beneath the macula. These newly formed blood vessels frequently bleed, causing the macula to bulge or form a mound, often surrounded by small hemorrhages and tissue scarring.<sup>7</sup> The results are a distortion in central vision and the appearance of dark spots. While the progression of atrophic AMD may take place over years, neovascular AMD can progress in mere months or even weeks.<sup>8</sup>

#### Genetics

Research has shown that age-related macular degeneration is a disease with multiple risk factors. Studies of families with age-related macular degeneration showed some genetic component and inheritance pattern to the disease.<sup>9,10</sup> Identical twins with age-related macular degeneration and common environmental and dietary influences show a strikingly similar appearance and degree of visual loss (89–100%). Fraternal twins reared in a shared environment show less visual loss (46%).<sup>11</sup>

Recently, research has identified a gene responsible for age-related macular degeneration.<sup>69-71</sup> This genetic abnormality is present in approximately 50% of patients with age-related macular degeneration. The responsible genes affect the body's ability to suppress inflammation. The specific defect is of the “complement system” of the inflammatory pathway. This defect allows the body to mount an abnormally exuberant inflammatory response, especially in the retina. Over many years, inflammation is thought to cause damage and degeneration to the retina, thereby affecting vision.

Currently, there is no widely available test for this gene mutation. Nevertheless, genetic testing may become available in the near future.

### ETIOLOGY AND MECHANISMS OF ACTION

#### General Causes

The causes of AMD are currently unknown. One theory postulates that abnormalities in the enzymatic activity of aged retinal pigment epithelium (RPE) cells lead to accumulation of metabolic byproducts. When the RPE cells become engorged, their normal cellular metabolism is obstructed, resulting in extracellular excretions that produce pigment deposits—drusen—and lead to neovascularization.<sup>12</sup>

A more recent theory suggests an alteration in the dynamics of the choroidal blood circulation as an important pathophysiological mechanism. The choroid is the system of blood vessels adjacent to the retina; the retina itself contains no blood vessels. Blockages within the choroidal blood vessels lead to increased ocular rigidity and decreased efficiency in the choroidal blood circulation system. Specifically, the increased capillary resistance due to blockages causes elevated hydrostatic pressure, resulting in the release of proteins and lipids extracellularly, forming basal deposits, primarily as drusen.<sup>13</sup> Along with drusen formation, there may be deterioration in the elastin and collagen in Bruch's membrane—i.e., the barrier between the retina and the choroids—causing calcification and fragmentation. This, coupled with an increase in vascular endothelial growth factor (VEGF), allows the growth of choriocapillaries into the retina that have passed through the fractured Bruch's membrane.<sup>14</sup>

The depositing of drusen is generally believed to be the precursor lesion for AMD when they are “soft” or “indistinct” ( $\geq 63 \mu\text{m}$ ). Small drusen ( $< 63 \mu\text{m}$ ) are extremely common, with approximately 80% of the general population over 30 manifesting at least one. As one ages, there is an increase in the number of drusen and the amount of confluence of drusen—i.e., aggregation. After age 70, 26% of individuals have soft drusen and 17% have confluent drusen.<sup>15</sup>

## Contributing Causes

**Cigarette Smoking** It is widely believed that cigarette smoking is associated with AMD. Cigarette smoking among women increases the risk of macular degeneration by 2.4-fold. Those who quit smoking still have a twofold increased risk. Among those who quit smoking for 15 years, little reduction in risk was shown. Cigarette smoking is an independent and avoidable risk factor for age-related macular degeneration among women.<sup>16</sup>

**Oxidative Stress** Oxidative stress that reduces blood flow to the eye and increases the level of free radicals is a contributing factor to both wet and dry macular degeneration. This occurs when naturally occurring antioxidants are present in decreased concentrations. Diminished levels of glutathione occur during aging, which makes the lens nucleus susceptible to oxidative stress-induced clouding.<sup>17</sup> Decreased vitamin C, normally highly concentrated in the aqueous humor and corneal epithelium, is less effective in helping absorb ultraviolet radiation and preventing cataracts than when present in high concentration.<sup>18</sup> L-carnosine and vitamin E also mitigate oxidative stress and free-radical damage.

**Inflammation** Retinal pigment epithelium (RPE) and, possibly, choriocapillary injury and inflammation lead to the formation of an abnormal extracellular matrix, which causes an altered and abnormal diffusion of nutrients to the retina and RPE, possibly precipitating further RPE and retinal damage.<sup>19</sup>

**Phototoxicity** Another risk factor for AMD is phototoxicity caused by exposure to blue and ultraviolet radiation, which adversely affects the functioning of RPE cells. Blue-light irradiation destabilizes certain membrane structures in RPE cells.<sup>20</sup> Exposure to sunlight without protective sunglasses is a risk factor for AMD.

**Arterial Hypertension** Men with a history of hypertension are at greater risk for developing AMD.<sup>21</sup> Prolonged treatment of hypertension with a thiazide diuretic, however, was associated with a more significant incidence of neovascular AMD.<sup>22</sup>

**Nutrient Deficiencies** Deficiencies in the carotenoids lutein, zeaxanthin, and meso-zeaxanthin are linked to AMD. Lutein, zeaxanthin, and meso-zeaxanthin are present in the retina and positively affect macular pigment density. Lutein and zeaxanthin are important in the prevention of AMD by maintaining denser macular pigment; this results in less retinal tearing or degeneration.<sup>23</sup> The therapeutic efficacy of lutein and zeaxanthin in AMD is significant, according to the Lutein Antioxidant Supplementation Trial (LAST), which showed improvement in several symptoms accompanying AMD.<sup>24</sup>

**High Fat Intake** Higher intake of specific types of fat rather than total fat intake may be associated with a greater risk for advanced AMD. Diets high in omega-3 fatty acids and fish were inversely associated with risk for AMD when intake of linoleic acid (an omega-6) was low.<sup>25</sup>

## ANATOMY AND PHYSIOLOGY (STRUCTURE AND FUNCTION)

### The Retina and the Choroid

The retina is the innermost layer of the eye and is comparable to the film inside a camera. It is composed of nerve tissue that senses light entering the eye. This complex system of nerves sends impulses through the optic nerve to the brain, which translates these messages into the images we see. (We “see” with our brains; our eyes merely collect the information to do so.)<sup>26</sup>

The retina is composed of numerous layers (10 in all), including (from the innermost layer next to the vitreous humor) nerve cells that connect the eye to the optic nerve and the brain, the cones and rods that contain photoreceptors, and a retinal pigment epithelium (RPE) layer. Beneath the RPE are another four layers: closest to the RPE is Bruch's membrane, which separates the RPE from the choroid; then the choroid itself, which is made up of a system of blood vessels and pigment cells. There are two

layers of the choroid: the tiny capillaries closer to the RPE, called the choriocapillaries, and the larger blood vessels. Outside the choroid is the sclera, the white part of the eye.<sup>27</sup>

In the central part of the retina is the macula. The macula is made up predominantly by cone cells containing photoreceptors most sensitive to light, color, and visual detail. The other type of photoreceptors, the rods, is found on the periphery of the macula, with many occupying the space outside the macula. The rods detect motion as well as dim and night light.<sup>13</sup>

### **Visual Pathways**

Light entering the eye is converged first by the cornea, then by the crystalline lens. The light rays intersect at a point just behind the lens (inside the vitreous humor) and diverge from that point back to the retina. The diverging light passes through nine (clear) layers of the retina and, ideally, is brought into focus in an upside-down image on the first (outermost) retinal layer (pigmented epithelium). The image is reflected back onto the adjacent second layer, where the rods and cones are located. Rods and cones actually face away from incoming light, which passes by these photoreceptors before being reflected back onto them. Light causes a chemical reaction with “iodopsin” in cones and with “rhodopsin” in rods, beginning the visual process that continues by transmission through nerve-cell complexes to the optic nerve and the brain.<sup>13,26</sup>

## **PATHOPHYSIOLOGY**

The pathophysiological mechanisms causing AMD are not well understood. Normal aging results in changes in the macula, including a reduction in light-sensitive cone and rod cells (photoreceptors) and granules of pigment in the retinal pigment epithelium (RPE).<sup>29</sup> The pigment granules of the RPE absorb incoming light and reflect it back to the cones and rods. Progression of these processes is more rapid and severe in AMD than in healthy eyes and usually is accompanied by increased waste products in the RPE that adversely affect the retina. The barrier between the retina and the choroid, known as Bruch’s membrane, which is normally elastic, becomes laden with debris deposited from the adjacent RPE. This causes a fragile and fractured Bruch’s membrane—one unable to assimilate incoming debris.<sup>7</sup>

These pathophysiological changes result in production of larger and less well-demarcated drusen—the pigmented deposits occurring under the macula. These larger drusen are in contrast to the smaller and better-demarcated drusen found in healthy eyes of people over 30. Large drusen ( $\geq 63\mu\text{m}$ ) are characteristic of atrophic AMD, in which this drusen causes thinning of macular tissue, experienced as blurry or distorted vision with possible blank spots in central vision.<sup>15</sup>

Changes in the retina can result in the abnormal growth of very tiny blood vessels in the choroid, known as choriocapillaries, which grow into the retina beneath the macula. This process of choroidal neovascularization is the essential mark of more severe and debilitating neovascular AMD, in which abnormal bulges appear in the macula because of the growth of blood vessels in the retina. The condition frequently worsens, because these blood vessels leak and form scar tissue.<sup>29</sup> Neovascular AMD is characterized by distorted vision: The normally smooth macula becomes bumpy and contains blank spots in central vision. The onset can be very rapid compared with atrophic AMD, and more debilitating, with almost the complete loss of central vision in some cases.<sup>12</sup>

The underlying pathophysiological changes of AMD may be a breakdown in normal enzymatic activity of aging retinal pigment epithelium (RPE) cells or dysfunction of the choroidal vascular system that results in increased ocular rigidity and decreased efficiency in the choroidal blood circulation. The aging eye may fail to break down and remove old proteins that accumulate and crosslink, forming glycation end-products.<sup>30</sup> The deterioration of macular cones is a possible underlying cause for AMD.<sup>31</sup>

## **PHARMACOLOGY**

Historically, there has been little within conventional medicine to restore eyesight lost to either form of the disease. Several new therapies are showing promise, however.

### **Hydergine**

Hydergine is a mild vasodilator used to stimulate mental functioning and shown effective in treating dry macular degeneration in doses of 4–5 mg per day and higher.<sup>32</sup>

### **Thalidomide**

Several new antiangiogenesis drugs that inhibit neovascularization have been developed that demonstrate the beneficial effects of thalidomide and prednisolone. Thalidomide, in particular, may be the most promising in counteracting the progression of neovascularization in wet AMD patients by inhibiting VEGF.<sup>33</sup> It is legal for doctors to prescribe thalidomide to treat wet macular degeneration, even though it is only officially approved and indicated to treat leprosy. Thalidomide causes severe birth defects and must not be used by pregnant women or women who may become pregnant.

### **Anti-VEGF Medications: Macugen®, Lucentis®, and Avastin®**

Anti-VEGF medications are a new treatment for wet macular degeneration. VEGF is an acronym for vascular endothelial growth factor. VEGF is a small molecule that acts as a signal to cause human cells to act in certain ways. There are many types of VEGF

molecules normally found in the human body. VEGF's main role is to induce new blood vessel formation. It also functions to increase inflammation and cause fluid to leak out of blood vessels. In wet macular degeneration, VEGF stimulates the formation of abnormal blood vessels in the macular area of the retina. These blood vessels are abnormally porous and can bleed, which can lead to loss of vision.

All the anti-VEGF medications work in a similar fashion. They chemically bind to and inhibit (or prevent) the biologic activity of VEGF. By preventing VEGF's action, they effectively reduce and prevent the formation of abnormal blood vessels. They also reduce the amount of leakage and therefore reduce swelling in the macula. These actions lead to preservation of the vision in patients with macular degeneration.

There are three types of anti-VEGF medications currently being used. The first agent is called pegaptanib, or Macugen®. It selectively binds to a specific type of VEGF called VEGF 165, one of the dangerous forms of VEGF.<sup>72</sup> Macugen® has been approved by the Food and Drug Administration (FDA) for treatment of wet AMD. It is administered via intraocular injection given every six weeks.

Lucentis®, or ranibizumab, is also FDA-approved for the treatment of wet macular degeneration. As opposed to Macugen®, Lucentis® inhibits all forms of VEGF. Lucentis® is administered via monthly intraocular injection.

A third anti-VEGF agent currently in use is Avastin®, or bevacizumab. Avastin® is chemically similar to Lucentis® and works via the same mechanism to inhibit all forms of VEGF. This drug is commonly used but is not approved by the FDA. The cost of Avastin® is approximately 90% less than the other two agents. There is a clinical trial underway sponsored by the National Eye Institute. This study is evaluating the safety and efficacy of Avastin® over against Lucentis®. The results will not be available for years.

Untreated, most patients with wet macular degeneration will get worse and lose their central vision.<sup>73</sup> Although the mechanisms of action of the anti-VEGF agents are similar, the success rates between the treatments vary. Macugen® was the first anti-VEGF treatment on the market. Macugen® was shown to allow patients a better chance of keeping their vision. Seventy percent of patients taking Macugen® did not have further severe visual loss.<sup>73</sup> In other words, Macugen® patients were found to lose less vision. Macugen® has not been found to improve vision.

Lucentis® improved on the results of Macugen®. Ninety-five percent of Lucentis® patients kept their vision, and nearly 40% of Lucentis® patients improved. Forty percent of patients completed one year of treatment with vision of 20/40 or better.<sup>74</sup>

Avastin® has not been as thoroughly investigated as either Lucentis® or Macugen®.<sup>75</sup> Many retina specialists believe that Avastin®'s efficacy parallels that of Lucentis®.<sup>76</sup> Rigorous clinical trials for Avastin® are underway and are being performed by the National Eye Institute.

Lucentis®, Macugen®, and Avastin® are all administered by intraocular injection—in other words, these medications are injected directly into the eye. The injections are given after the surface of the eye has been cleansed and sterilized. Some doctors will give antibiotic drops prior to the injection. Some form of anesthesia is usually administered. This can be given in the form of drops or as a very small injection of anesthetic around the eye. The actual injection takes a few seconds.

Possible adverse effects of intraocular injections occur at a rate of fewer than 1 per 100 injections.<sup>74</sup> When adverse effects occur, however, they can be very serious and sight-threatening. One possible adverse reaction is a serious eye infection known as endophthalmitis. Other possible complications are a retinal detachment and the development of a cataract. High ocular pressure usually follows the injection but generally resolves within the hour.

It is rare to have a systemic side effect after an intraocular injection. Yet there is some evidence that there may be a slight increased risk of a stroke after Lucentis® injections.<sup>77</sup> Further data is currently being collected and analyzed. Unlike Macugen® and Lucentis®, Avastin® has not had extensive formal testing for side effects and complications.

From a patient's point of view, it is very important to understand certain concepts of wet macular degeneration and its treatment in order to be able to discuss a therapeutic plan with his or her doctor. A specific treatment plan should be tailored to each patient's needs and disease activity. Review all the treatment options for wet macular degeneration: conventional laser, photodynamic therapy, and anti-VEGF treatments. Each treatment has a different risk/benefit profile. Some of the treatments can be used in combination to produce an effect greater than an individual treatment alone.<sup>78</sup> The anti-VEGF treatments have been a breakthrough in terms of better outcomes for patients with wet macular degeneration.

## **Current AMD Treatments**

**Laser Photocoagulation** Laser photocoagulation (LP) is effective in the treatment of eyes with exudative disease but has not

worked well on atrophic AMD due to neovascularization. LP is limited to the treatment of well-defined, or "classic," subretinal neovascularization; present in only 15% of those with exudative disease.<sup>34</sup> Most patients have subretinal neovascularization that is "occult" (i.e., covered by blood or thick subretinal fluid). In eligible eyes, LP can reduce the risk of further vision loss, but it does not restore lost vision. After the successful treatment of bleeding vessels, choroidal neovascularization can recur and cause further vision loss.<sup>7</sup>

**Photodynamic Therapy** Photodynamic therapy is the newer and more widely preferred treatment that takes advantage of certain unique properties of subretinal neovascular vessels. Compared with normal blood vessels, neovascular tissue appears to retain the dye used in photodynamic therapy. After dye has been injected in a peripheral vein, it is "excited" with laser light. This activated dye then forms reactive free radicals that close down the leaky subretinal vessels. Because normal retinal vessels retain very little dye, the abnormal subretinal vessels are selectively "damaged."<sup>35</sup>

In some studies, one dye, verteporfin (Visudyne), was shown to preserve vision in a significant number of patients with the wet form of AMD. Researchers have reported that Visudyne has prevented vision loss in 61% of wet AMD patients receiving it in experimental trials.<sup>36</sup> Visudyne therapy is approved for the treatment of classic subfoveal choroidal neovascularization (CNV) lesions. The lesion size must measure less than 5400  $\mu\text{m}^2$  at the time of treatment.<sup>37</sup>

**Surgery** Subretinal surgery has been attempted for age-related macular degeneration. Some surgeries were geared toward the removal of blood and the subretinal neovascular membrane. Another type of surgery tried to physically displace the macula and move it onto a bed of healthier tissue. Overall, research studies show that the results of surgery are disappointing.<sup>79</sup> Vision has generally not improved after surgery.<sup>80</sup> Additionally, the frequency and severity of surgical complications were generally thought to be unacceptably high.

## NUTRITIONAL THERAPY

### Recommended Foods

**Foods Containing Lutein and Zeaxanthin** The phytochemicals that protect against wet macular degeneration are lutein and zeaxanthin.<sup>38-43</sup> Lutein is a pigment found in dark green leafy vegetables, including spinach, kale, broccoli, and collard greens. Zeaxanthin is found in fruits and vegetables with yellow hues, such as corn, peaches, persimmons, and mangoes. Meso-zeaxanthin is not found in foods but is produced in the retina from ingested lutein.

Because lutein and zeaxanthin have the tissue-specific characteristic of all carotenoids, their natural tendency is to concentrate in the macula and retina. Consumption of foods rich in these substances is especially important, as they have a direct effect on macular pigment density: The denser the pigment, the less likely a retinal tear or degeneration will occur. Some improvement has been seen in subjects after only one month of supplementation.<sup>23,43</sup>

**Soy** Soy contains the phytochemical genistein, which has antiangiogenesis properties.<sup>44</sup> This property of inhibiting blood vessel growth is important in limiting abnormal ingrowth of choroidal blood vessels. Those with neovascular macular degeneration may take two Ultra Soy Extract capsules 2 times per day to obtain enough genistein to possibly inhibit blood vessel growth in the eye.

**Oily Fish** Oily fish like salmon, tuna, and mackerel are important sources of omega-3 fatty acids, essential for protection against macular degeneration and other diseases.<sup>25,45</sup> More frequent consumption of fish protects against late age-related macular degeneration. The greatest benefit was seen in those who ate one serving a week; more fish did not offer more protection.<sup>45</sup>

### Dietary Supplements

**Bilberry Extract** Positive results have been noted in studies using bilberry for macular degeneration, and other eye disorders, including, diabetic retinopathy, retinitis pigmentosa, glaucoma, and cataracts. Bilberry contains anthocyanidins, a blue plant pigment, which protect and regenerate retinal purple (rhodopsin).<sup>46</sup> There may be additional benefits by adding vitamin E.<sup>47</sup> The anthocyanidins in bilberry decrease vascular permeability by interacting with blood vessel collagen so as to slow down enzymatic attack on the blood vessel wall. This may prevent leakage from capillaries; prevalent in neovascular AMD.

**Ginkgo Biloba** Ginkgo biloba improves microcapillary circulation in the eye and slows down deterioration of the macula.<sup>48</sup> It increases blood flow by inhibiting platelet aggregation and regulating blood vessel elasticity; improving blood flow through major blood vessels and capillaries. Ginkgo is a powerful antioxidant.<sup>49</sup>

**Note:** For more information see the Safety Appendix

**Grape Seed Extract** Grape seed extract is a powerful antioxidant, classified as one of the bioflavonoids. Bioflavonoids derived from plants are readily assimilated into our body when consumed. Bioflavonoids have the ability to strengthen blood vessel walls within a short time after ingesting them.<sup>50</sup>

### Recommended Antioxidants

**Glutathione and Vitamin C** Glutathione and vitamin C are antioxidants found in high concentrations in the healthy eye and in diminished quantities in AMD patients. Vitamin C aids in glutathione synthesis in the eye. When it is combined with cysteine, an amino acid antioxidant, cysteine remains stable in aqueous solutions and is a precursor to glutathione synthesis. Vitamin C is important because it absorbs ultraviolet radiation and prevents cataracts.<sup>18</sup>

**L-Carnosine** L-carnosine is a naturally occurring antioxidant and anti-glycation agent. Topically applied N-acetyl-carnosine prevented light-induced DNA strand breaks and repaired damaged DNA strands.<sup>51</sup>

**Riboflavin, Taurine, and Lipoic Acid** Other antioxidants for protection against AMD are riboflavin monophosphate, taurine, and R-dihydro-lipoic acid. Riboflavin monophosphate is a B complex vitamin that reduces oxidized glutathione and helps to prevent sensitivity to light, loss of visual acuity, and burning and itching in the eyes.<sup>52</sup> Taurine is an amino acid found in high concentrations in the retina. A deficiency of this amino acid alters the structure and function of the retina.<sup>53</sup> R-dihydro-lipoic acid is considered a "universal antioxidant" because of the fact that it is fat and water soluble.<sup>54</sup>

**Selenium** Selenium, an essential trace mineral, is a component of the antioxidant enzyme, glutathione peroxidase, important in slowing the progression of AMD and other eye disorders including, cataracts and glaucoma.<sup>55,56</sup>

**Note:** For more information see the Safety Appendix

**Coenzyme Q10** Coenzyme Q10 (CoQ10) is an important antioxidant that may be beneficial in protecting against free radical damage within the eye.<sup>57</sup> In one study a mix of antioxidants including CoQ10, acetyl-L-carnitine, polyunsaturated fatty acids and vitamin E improved the function of mitochondria in retinal pigment epithelium.<sup>58</sup> Mitochondrial dysfunction in the eye and throughout the body produces damaging reactive oxygen species, believed to be the cause of many diseases and aging.<sup>59</sup>

### **Age-Related Eye Disease Study: Supplement Recommendations**

The largest and most important study on the relationship of nutritional supplements and AMD is the Age-Related Eye Disease Study (AREDS). AREDS was the first large study to show a benefit of anti-oxidant and zinc supplementation on the progression of AMD and associated vision loss. Thousands of patients were followed for over six years. AREDS revealed significant improvements for patients with AMD and recommended antioxidants plus zinc (with copper) for most patients with AMD, except for advanced cases in both eyes. The AREDS recipe consists of the following daily: Vitamin A (Beta Carotene), Vitamin C, Vitamin E, Zinc and Copper.<sup>60</sup>

**Note:** For more information see the Safety Appendix

## **FUNCTIONAL AND PRACTICAL MEDICINE**

### **The Importance of the Macular Pigments: Lutein, Zeaxanthin, and Meso-zeaxanthin**

The relation between the density of macular pigment and the onset of AMD is well-established. Ocular pigments are essential in the healthy functioning of the eye, and specifically in protecting and maintaining the macula. These pigments are central to the photoreceptor mechanism that picks up the light focused on the macula. They are found in the cone and rod cells within the macula, retina pigment epithelium (which first absorbs the light entering the retina), and surrounding tissues, including blood vessels and capillaries of the choroid which nourish the retina.<sup>42</sup>

Lutein and zeaxanthin ensure proper functioning of the macula by filtering out harmful blue and ultraviolet light and by acting as antioxidants.<sup>38,39</sup> During the aging process, there is a decrease in levels of lutein and zeaxanthin. Low levels of macular pigments are linked to AMD. Inadequate concentrations of lutein and zeaxanthin are associated with development of abnormal pigment deposits under the macula (large drusen); the consequent thinning of the macula; and with choroidal neovascularization, which can lead to very serious and rapid visual impairment.<sup>43</sup>

It is important to raise macular concentrations of lutein and zeaxanthin with foods rich in these carotenoids or dietary supplements containing them. Intake of lutein and zeaxanthin is an important preventative measure, but may also reverse the degeneration process when it is ongoing.<sup>24</sup> Fruits with a yellow or orange color, like mangoes, kiwis or oranges, and vegetables of the dark green leafy variety and orange and yellow types are food sources of lutein and zeaxanthin.<sup>40</sup> Egg yolk is a good dietary source of these carotenoids.

If all people had to do was consume adequate zeaxanthin and lutein, then macular degeneration would theoretically disappear as an age-related disorder. Regrettably, macular degeneration still occurs in aging individuals, even in some of those who regularly eat fruits, vegetables, and eggs. In what may be a breakthrough in the prevention of the blinding epidemic of macular degeneration, scientists have discovered a compound called meso-zeaxanthin that is naturally produced in the retina and is needed to maintain youthful macular density.<sup>62</sup> They now know that the macular pigment is comprised of the following three carotenoids: 50% lutein, 25% zeaxanthin, and 25% meso-zeaxanthin.

Unlike lutein and zeaxanthin, meso-zeaxanthin is not found in the diet, but is converted in the retina from ingested lutein.<sup>62</sup> If taken as a supplement, meso-zeaxanthin is absorbed into the blood stream and effectively increases macular pigment levels.<sup>63</sup> Patients with macular degeneration have been shown to have 30% less meso-zeaxanthin in their macula compared to healthy eyes.<sup>64</sup> One reason for this deficiency of meso-zeaxanthin is lack of ingested lutein. Another explanation for the missing meso-zeaxanthin observed in macular degeneration may be the inability to adequately convert lutein to meso-zeaxanthin in the retina.

An autopsy study on donated eyes was done to measure levels of lutein, zeaxanthin, and meso-zeaxanthin in the retina of those with and without macular degeneration. As expected, levels of all three carotenoids (lutein, zeaxanthin, and meso-zeaxanthin) were reduced in those with macular degeneration compared to control subjects. The most significant finding, however, was the sharp decrease in meso-zeaxanthin in relation to zeaxanthin in the macula of macular degeneration subjects.<sup>65</sup> This postmortem study helped confirm other studies indicating the importance of all three carotenoids (lutein, zeaxanthin, and meso-zeaxanthin) in maintaining the structural integrity of the macula.<sup>66,67</sup> These carotenoids protect the macula and the photoreceptor cells beneath via their antioxidant properties and light-filtering capabilities.<sup>68</sup>

Scientists believe that people who have a high intake of lutein and zeaxanthin (from either diet or dietary supplements) and take supplemental meso-zeaxanthin will have a very low incidence of macular degeneration.

## Free Radicals and Antioxidants

Antioxidants are vital components in maintaining the health of the eye and the body. Antioxidants work by scavenging free radicals from the body. Free radicals are simply oxygen atoms that have lost an electron through the body's normal metabolic processes. The free radicals quickly attach nearby body tissues to stabilize themselves. This consequently takes an electron from that tissue, producing yet another free radical which perpetuates the chain reaction. This cascade of oxidation is a process known as oxidative stress.

Antioxidants are chemically structured so that they are able to donate electrons freely without altering their valence (since their electrons are not paired). This means that antioxidants can stabilize or trap free radicals without themselves becoming dangerous free radicals themselves. Antioxidants will donate electrons until they have no more. Because many of these antioxidants can be regenerated (reduced) through the acceptance of free electrons available during normal metabolism, one antioxidant molecule is able to neutralize many free radicals.

While free radicals are produced during normal metabolism, this production is accelerated by smoking and exposure to second-hand smoke<sup>16</sup> and by diets high in saturated fats, cholesterol, and low in the "good fats" found in fish such as salmon and tuna, whole grains, and legumes.<sup>25</sup> Smoking and a high-fat diet are associated with AMD.

AMD is associated with decreased levels of natural antioxidants in the healthy eye. These include glutathione and vitamin C, and the carotenoids, lutein and zeaxanthin.<sup>18,42</sup> Dietary supplementation with these antioxidants is important in slowing the progression of AMD. Other recommended antioxidants beneficial to the macula and retina are vitamin A, vitamin E, L-carnosine, taurine, lipoic acid, selenium, zinc (with copper) and grape-seed extract, and coenzyme Q10.

**Note:** For more information see the Safety Appendix

## Protection against Ocular Atherosclerosis

Many experts believe the underlying cause of AMD occurs in the choroids.<sup>7</sup> The choroid lies underneath the retina and provides it with oxygen and nutrients. The retina contains very few blood vessels. The onset of AMD is associated with choroidal blood vessel damage, frequently due to atherosclerotic plaque. This raises blood pressure within these vessels and results in an abnormal production of protein and fats that are deposited underneath the macula as pigment deposits called drusen. There is an associated problem of fracturing and loss of natural elasticity in the barrier between the retina and choroid, which facilitates abnormal growth of choroidal blood vessels into the retina, called choroidal neovascularization (CNV).

To protect against the deterioration of the blood circulatory network within the eye, a number of dietary supplements are beneficial. These include bilberry extract, Ginkgo biloba, grape-seed extract, and genistein. Bilberry helps protect blood vessel walls and leakage of capillaries, very common in neovascular AMD.<sup>46</sup> Ginkgo biloba improves blood flow through major blood vessels and capillaries, improving microcapillary circulation in the choroid by inhibiting plaque accumulation and maintaining elasticity of blood vessels.<sup>49</sup> Grape-seed extract strengthens blood vessels, even shortly after ingestion.<sup>50</sup> The phytochemical, genistein, found in large concentrations in soy, inhibits blood vessel growth necessary for the progression of neovascular AMD.<sup>44</sup>

Hydergine and thalidomide control blood vessel deterioration. Hydergine is beneficial in treating dry macular degeneration due to its ability to keep blood vessels open.<sup>32</sup> Thalidomide inhibits blood vessel growth, counteracting the progression of neovascularization in neovascular (wet) AMD. It is legal for doctors to prescribe thalidomide to treat wet macular degeneration even though it is only officially approved to treat leprosy.<sup>33</sup> It should be noted that thalidomide causes severe birth defects and must not be used by pregnant women or women who may become pregnant.

Lucentis® and Macugen® inhibit the action of vascular endothelial growth factor (VEGF), thus prevent the formation of abnormal blood vessels, reduce swelling in the macula, and help preserve vision. Another promising VEGF-inhibitor, Avastin®, is undergoing clinical trials for use in wet macular degeneration.

## Supplement and Drug Recommendations

To ensure that adequate concentrations of the essential macular pigments lutein, zeaxanthin, and meso-zeaxanthin are maintained, the following are suggested:

- Lutein Plus with high potencies of lutein, zeaxanthin, and other carotenoids may help slow the progression of advanced AMD into blindness.
- Super Zeaxanthin with Lutein and Meso-zeaxanthin

To protect and preserve the macular pigments from potentially damaging blue and ultraviolet radiation, the following protective eyewear is recommended:

- Life Extension's Solarshield sunglasses

To protect against the damaging effects of free radicals on the retina, and the macula in particular, the following antioxidants and antioxidant mixes are suggested:

- Vitamin A (Beta Carotene)
- Vitamin C
- Vitamin E
- Zinc
- Copper
- Lipoic acid
- Selenium
- Riboflavin
- Taurine
- Coenzyme Q10
- Life Extension Mix
- Life Extension Booster
- Brite Eyes II eye drops for antioxidant (vitamins A and E), anti-glycating protection (N-acetyl- carnosine)
- Super EPA/DHA with Sesame Lignans

To help protect against the onset and progression of blood vessel damage in the eye that leads to AMD, the following are recommended:

- Ginkgo biloba extract
- Grape seed-skin extract
- Bilberry extract
- Super Absorbable Soy Isoflavones for genistein
- Hydergine (prescription only)
- Lucentis® (prescription only)
- Macugen® (prescription only)
- Avastin® (prescription only)

## SUMMARY

### Scientific Summary

This protocol has provided background on age-related macular degeneration in terms of its nature, etiology, underlying physiology, pathophysiology, pharmacology, and nutrition. Basic information has been provided on AMD, including newer standard and non-standard approaches to treating this disease. The protocol has focused on the importance of nutritional solutions that prevent or treat AMD. Enough background information has been presented on AMD and its nutritional supplements to enable the reader to make informed decisions on the usefulness of nutrition and its effects on AMD.

There has been limited success within conventional medical treatment protocols to restore lost eyesight from either form of AMD. Leading researchers are documenting the benefits of more holistic approaches to AMD. Patients are encouraged to increase physical fitness, improve nutrition (including a reduction in saturated fats), abstain from smoking, and to protect their eyes from excessive light. Dietary supplementation with trace elements, antioxidants, and vitamins is recommended for improving overall metabolic and vascular functioning. Early screening and patient education offer the most hope for reducing the debilitating effects of the disease.

### Functional Summary

The best approach to ensuring protection against the onset of age-related macular degeneration and the possible treatment of the condition involves an understanding of some of the main circumstances under which the condition arises. These are presented below followed by the recommended nutritional therapies for each problem.

1. A reduction in the essential macular pigments lutein, zeaxanthin, and meso-zeaxanthin, critical for the protection and proper functioning of the mechanisms required for the detection and imprinting of the light signals that come into the macula from the outside world.

As lutein, zeaxanthin, and meso-zeaxanthin are the essential pigments within the macula, it is critical to replenish them as they become depleted through the aging process. Consumption of foods rich in these substances is especially important since they have

a direct effect on macular pigment density. When the pigment in the macula is denser, retinal tearing or degeneration is less likely. Lutein and zeaxanthin are found in yellow or orange vegetables, in dark leafy greens, and in fruits with yellow or orange hues. Egg yolk is a good source of lutein. Meso-zeaxanthin is not available through dietary sources, but can be manufactured in the retina from ingested lutein. Dietary supplements of lutein, zeaxanthin, and meso-zeaxanthin are recommended.

2. A reduction in antioxidant levels within the retina and surrounding structures that make possible the presence and proliferation of free radicals that damage these structures and keep them from optimal functioning.

An increase in damaging free radical activity occurs through smoking, exposure to second-hand smoke, in diets high in saturated fats, cholesterol, and low in the “good fats” found in fish, whole grains and legumes. Smoking and high-fat diets are associated with AMD.

Decreased levels of natural antioxidants in the healthy eye are associated with AMD. Some of these essential natural antioxidants are glutathione, vitamin C, and the carotenoids, lutein and zeaxanthin. Dietary supplementation with these antioxidants protect against the progression of AMD. Other recommended antioxidants to protect the macula and retina include vitamin A, vitamin E, L-carnosine, taurine, lipoic acid, selenium, zinc (with copper), grape-seed extract, and coenzyme Q10.

3. The onset of ocular atherosclerosis involves blockages in the choroidal blood vessels that adversely affect the functioning of the retina and, particularly, the macula.

Damaged blood vessels in the eye are associated with the onset of AMD. Blockages of these blood vessels, known as ocular atherosclerosis, raises blood pressure, creates deposits under the macula, and abnormal growth of blood vessels into the retina (choroidal neovascularization). The result is severe and debilitating neovascular AMD.

Dietary supplements are beneficial in treating ocular atherosclerosis. These include bilberry extract, ginkgo biloba, grape-seed extract, and genistein. Bilberry protects blood vessel walls and reduces leakage of capillaries, common in neovascular AMD. Ginkgo biloba improves blood flow and inhibits plaque accumulation in the blood vessels of the eye and maintains the elasticity of blood vessels. Grape-seed extract strengthens blood vessel walls, even shortly after ingestion. The phytochemical genistein, found in soy, inhibits blood vessel growth, slowing the progression of neovascular AMD.

Hydergine and thalidomide help with ocular atherosclerosis. Hydergine dilates blood vessels, stimulates mental functioning, and is effective in treating atrophic AMD. Thalidomide inhibits blood vessel growth and counteracts the progression of neovascularization in AMD patients.

Lucentis® and Macugen® are approved for the treatment of wet macular degeneration. By inhibiting the action of vascular endothelial growth factor (VEGF), they prevent the formation of abnormal blood vessels, reduce swelling in the macula, and help preserve vision. Another promising VEGF-inhibitor, Avastin®, is undergoing clinical trials.

### General Precautions

Dietary supplements do not always positively affect health due to the systemic imbalances. Increasing evidence indicates that supplementation with one carotenoid may reduce serum levels of other carotenoids.<sup>61</sup> Because there are more than 50 naturally occurring carotenoids, it is important that the correct supplement or combination of supplements be chosen. Mega-doses, beyond the prescribed dosage, are generally discouraged. Consult with healthcare professionals knowledgeable in the uses, dosages, and interactive effects of supplements to ensure the best nutritional therapy is utilized.

## LIFE EXTENSION FOUNDATION RECOMMENDATIONS

- **Lutein Plus** with lutein, zeaxanthin is suggested at a dosage of 1 tbsp daily with a fatty meal
- **Super Zeaxanthin with Lutein and Meso-zeaxanthin**; 3.75 mg of zeaxanthin and meso-zeaxanthin and 10 mg of lutein per capsule, 1 or 2 capsules daily
- **Life Extension’s Solarshield sunglasses**
- **Lipoic acid**, 150-300 mg per day
- **Selenium**, 200-300 mcg per day
- **Riboflavin**, 50-150 mg per day
- **Taurine** is suggested at a daily dosage of 1,000 mg
- **Coenzyme Q10** – 100 to 300 mg per day
- **Life Extension Mix**, 9 tablets, 14 capsules, or 3 scoops per day in divided doses
- **Life Extension Booster**, suggested dosage of 1 capsule daily
- **Brite Eyes II** eye drops (N-acetyl-carnosine) is suggested at 1-2 drops in each eye daily
- **Super EPA/DHA with Sesame Lignans**, two soft gels daily (for the dry and wet types).

- **Ginkgo biloba extract**, 120 mg per day.
- **Grape seed-skin extract**, 200-300 mg per day
- **Bilberry extract**, 150 mg per day
- **Super Absorbable Soy Isoflavones** for genistein: 1 capsule twice per day.
- **Hydergine**, 4-5 mg per day (prescription only)
- **Lucentis®** (prescription only)
- **Macugen®** (prescription only)
- **Avastin®** (prescription only)

The Age-Related Eye Disease Study (AREDS) recommended recipe consists of the following dosages:

- **Vitamin A** (Beta Carotene), 25,000 IU daily
- **Vitamin C**, 500 mg daily
- **Vitamin E**, 400 mg daily
- **Zinc**, 80 mg daily
- **Copper**, 2 mg daily

**Note:** Many of the basic vitamins and minerals listed above can be found in the Life Extension Mix.

For more information see the Safety Appendix

#### **About the Author**

Robert Sachs, Ph.D. is a medical writer specializing in the therapeutic area of ophthalmology. He has prepared FDA submissions for new ophthalmologic devices and drugs and has worked in cutting-edge technology companies developing a range of products in the medical and environmental fields.

Direct your questions to the Life Extension Health Advisory staff at (800) 544-4440.

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