

# Natural Therapies for Ocular Disorders, Part One: Diseases of the Retina

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## ABSTRACT

Diseases of the retina are the leading causes of blindness throughout the world. Evidence points to potential benefit from nutritional and botanical interventions for the prevention and treatment of several of these conditions, including macular degeneration, diabetic retinopathy, retinopathy of the newborn, and retinitis pigmentosa. Epidemiological evidence points to the potential of antioxidant vitamins E and C, carotenoids, zinc, and selenium in the prevention and possible treatment of macular degeneration. In addition, dietary components such as red wine—high in important flavonoids—and fruits and vegetables high in carotenoids appear to offer some protection. While diabetic retinopathy can best be prevented by maintaining good blood sugar control, there are a number of nutrients and botanicals which may help prevent and treat retinopathy by inhibiting protein glycosylation, stabilizing collagen, decreasing capillary permeability, and providing important antioxidant effects. Extensive research on the use of vitamin E for the prevention of retrolental fibroplasia (retinopathy of the newborn), despite yielding promising results, has not resulted in incorporation of vitamin E into conventional standards of care protocols. Retinitis pigmentosa resembles the retinal damage seen in taurine-deficient cats. While patients with retinitis pigmentosa do not appear to be deficient in taurine, they appear to have faulty cellular uptake of this important amino acid. Disturbed utilization of vitamin A also appears to play a part in retinitis pigmentosa, and a subgroup of patients benefit from supplementation.

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## Introduction

During the past few decades numerous studies have been published on the efficacy of nutritional and botanical medicines in the prevention and treatment of ocular diseases, including macular degeneration, diabetic retinopathy, retinitis pigmentosa, cataracts, glaucoma, and others. Part One of this review will explore the research on diseases of the retina, including macular degeneration, retinopathy, and retinitis pigmentosa. Part Two (to be published in a future issue) will include a review of the literature on cataracts, glaucoma, and other non-retinal disorders.

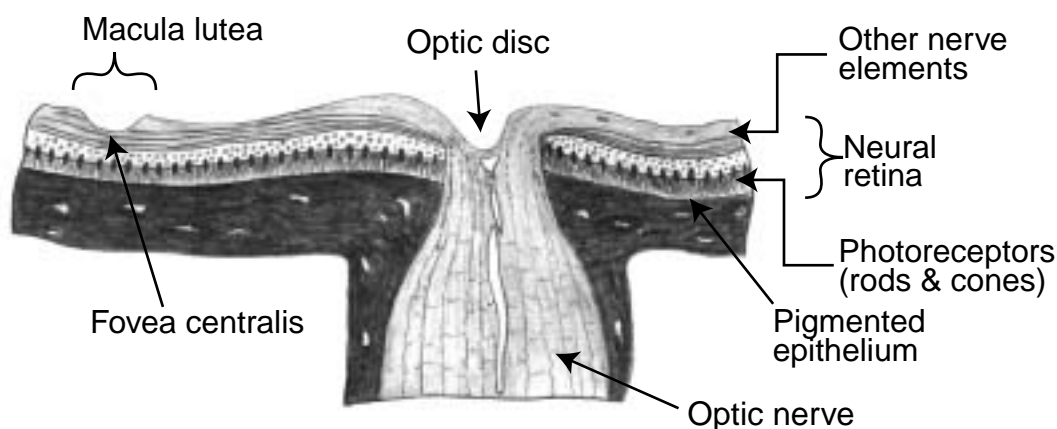
## Macular Degeneration

Age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness in older Americans. Laser photocoagulation therapy is effective in only a small percent of late-stage cases—those with neovascularization and exudates. Therefore, prevention is

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**Figure 1.** Elements of the Retina Involved in Macular Degeneration.



(PUFAs), particularly docosahexaenoic acid (DHA), especially in their outer segment membranes. DHA is readily oxidized in the oxygen-rich environment of the retina.<sup>6</sup>

Several of

of prime importance in reducing the health impact on this growing elderly population.

### Pathophysiology

Macular degeneration is characterized by atrophy of the macular disk. Tissues most effected are the photoreceptors and the retinal pigmented epithelium (RPE) (see Figure 1). The photoreceptors most sensitive to damage are the rods and the blue-light sensitive cones. Two types of AMD have been identified: an atrophic form, which involves pigmentary changes in the macula without hemorrhage or scar formation, and disciform macular degeneration, characterized by an exudative mound and sub- and intraretinal hemorrhage.<sup>1</sup> In both types the retinal pigment cells degenerate, with a resulting loss of rods and cones. Risk factors include family history of macular disease, cigarette smoking,<sup>2</sup> light exposure,<sup>3</sup> light iris pigmentation,<sup>4</sup> chemical exposure, history of cardiovascular disease, decreased hand grip strength, and hyperopia.<sup>5</sup>

### Antioxidants and AMD

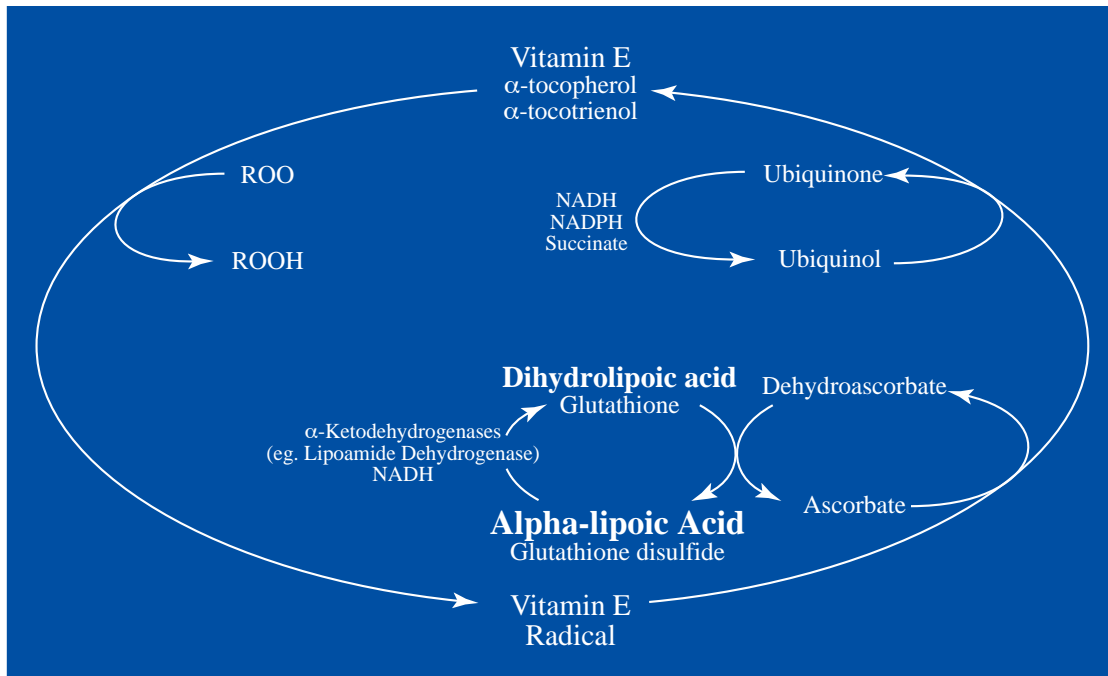
While the etiology of macular degeneration is not fully understood, evidence from animal studies points to the role of free radical damage from light exposure as a potential contributing factor. The photoreceptors of the eye are high in polyunsaturated fatty acids

of the known risk factors for AMD, including cigarette smoking and light exposure, appear to be at least partially related to oxidative stress.

Animal studies have demonstrated exposure to UV light, ionizing radiation, or visible light can lead to free radical formation and subsequent lipid peroxidation of the photoreceptor membranes. The resulting retinal damage is similar to that noted in humans with macular degeneration.<sup>7</sup> Antioxidants including vitamins C and E, and the carotenoids lutein and zeaxanthin, are found in high concentrations in the retina. Vitamin C is found in aqueous portions of cells throughout the retina, vitamin E in the photoreceptor outer segment membranes, and the carotenoids throughout the retina, but especially concentrated in the macula.<sup>7</sup>

Antioxidants enjoy a symbiotic, mutual recycling relationship in the retina (see Figure 2). Vitamin E, the major lipid-soluble antioxidant in the retina, scavenges peroxy radicals, yielding phenoxyl radicals which are then reduced by ascorbate, recycling vitamin E in the retina. Glutathione appears to be unsuccessful at recycling vitamin E in the absence of ascorbate. Dihydrolipoic acid enhances ascorbate's protective effect by regenerating it from dehydroascorbate.<sup>8</sup>

**Figure 2.** Vitamin E and Antioxidant Regeneration.



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not seem to provide protection.

### Vitamin E

The study cited above on 976 subjects also found high serum levels of vitamin E (as a-tocopherol) alone was protective for AMD.<sup>11</sup> The Physician's Health Study evaluated 21,120 individuals over a period of 12.5 years, none of whom had a diagnosis of AMD at the beginning of the study. Supplementation with vitamin E resulted in a 13-percent reduced risk of AMD (which was statistically insignificant).<sup>12</sup> Users of a multivitamin demonstrated a statistically insignificant 10-percent reduced risk.

Rat retinal studies have found low levels of vitamin A coupled with low levels of vitamin E appear to contribute to retinal damage similar to that seen in macular degeneration. Depressed levels of vitamin A in the presence of a vitamin E-free diet led to a five-fold increase in lipofuscin granule deposits in the pigment epithelial cells, marked disruption of photoreceptor outer segment membranes, and significant loss of photoreceptor cells (rods and cones equally). When vitamin A levels were higher, the same retinal damage without the loss of photoreceptor cells was in evidence.

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Therefore, vitamin C appears to protect against some of the damaging effects of light exposure. However, the catch-22 is that vitamin C levels have been found to decrease in retinas exposed to light.<sup>16</sup> Another animal study found vitamin C slowed the light-induced loss of photoreceptor cells.<sup>17</sup>

Vitamin C appears to protect the eye from light damage via its antioxidant effects. Rats exposed to bright light experienced deterioration of the rod outer segments (an effect similar to that which occurs in human AMD). Supplementation with ascorbate prevented loss of rhodopsin and preserved DHA, preventing its oxidation.<sup>18</sup> In this study, the protective effect of vitamin C occurred only if given prior to light exposure.

### Dietary Effects on AMD

The Beaver Dam Eye Study evaluated, via a food frequency questionnaire, the diets of 2,003 individuals age 43-84. The study found significant inverse associations between dietary intakes of carotenoids and vitamin E and the development of macular lesions – large drusen (subretinal pigment epithelial depos-

its) and other pigmentary abnormalities – consistent with future development of macular degeneration.<sup>19</sup> Other studies have also found intake of dietary carotenoids to be protective for AMD. Goldberg and associates at the University of Illinois, in analyzing the data from the first National Health and Nutrition Examination Survey (NHANES-1), found a negative correlation between intake of fruits and vegetables high in beta carotene and the development of AMD.<sup>20</sup> Seddon et al found a higher intake of spinach or collard greens was associated with a substantially lower risk for AMD.<sup>21</sup> Green leafy vegetables, as well as many other fruits and vegetables, are high in the carotenoid lutein which, as previously mentioned, is found in high concentrations in the retina, especially in the region of the macula.

Moderate wine consumption has been associated with a decreased risk for developing macular degeneration.<sup>22</sup> Assessment using the 3,072 adults, age 45-74, in NHANES-1 found nine percent of the group who consumed no alcohol developed AMD compared to only four percent in the group who drank wine. Protection appeared to be afforded even for those imbibing only about once a month. On the other hand, the Beaver Dam Eye Study found beer contributed to an increased risk for AMD in men.<sup>23</sup> Men who consumed at least 78 g/week or more of beer had a higher (borderline significant trend) five-year age-adjusted incidence of early AMD (10.6%) when compared to men who did not drink beer (6.9%). Drusen accumulation was associated with beer drinking in men.

### Minerals and AMD

Zinc is found in relatively high concentrations in the retina, particularly in the retinal pigment epithelium, and plays a significant role in several retinal enzyme systems, including retinol dehydrogenase and catalase.<sup>24</sup> Low dietary zinc levels appear to be related to an increased risk for developing AMD. Evalu-

ation of 1,968 participants in the Beaver Dam Eye Study found those in the highest versus the lowest quintile for dietary zinc intake had a lower risk for developing early macular degeneration.<sup>25</sup>

An *in vitro* examination of 114 donor retinas found soluble macular zinc levels declined by 45 percent in donors over age 70 when compared to donors under age 70. An even greater decline in zinc levels was noted in retinas which showed signs of macular disease.<sup>26</sup> Two case studies demonstrated a dramatic beneficial effect of a combination of IV and oral zinc and selenium in the treatment of macular degeneration.<sup>27</sup>

A double-blind, placebo-control study was conducted to investigate the effect of oral zinc supplementation on the progression of macular degeneration.<sup>24</sup> One hundred fifty-one subjects age 42-89 were assigned to receive either 100 mg zinc sulfate (providing 40 mg elemental zinc) daily or placebo (tablets containing lactose and fructose). All participants had ophthalmoscopically-diagnosed macular degeneration, absence of other serious eye diseases or metabolic disorders affecting vision, and visual acuity of 20/80 or better in at least one eye. The zinc-treated group demonstrated significantly less visual acuity loss than the placebo group during a 12-24 month follow-up. On funduscopy exam, significantly more subjects in the zinc-treated group remained stable or experienced a decrease in drusen accumulation when compared to the placebo group.

### The Carotenoid Connection

The carotenoids lutein and zeaxanthin are the two major components of macular pigment. The macula acquires its characteristic “yellow spot” appearance from the accumulation of carotenoid pigments. Lutein is found in higher concentrations away from the fovea, which is in the center of the macula,

**Table 1.** Dietary Sources of Lutein and Zeaxanthin.

|   |               |
|---|---------------|
| Egg yolk*   | Grapes        |
| Corn**  | Orange juice  |
| Orange Pepper***                                  | Zucchini      |
| Kiwi  | Yellow squash |
| Spinach and other dark green leafy vegetables**** |               |

\* egg yolk and corn have the highest lutein and zeaxanthin (85% of total carotenoids content)  
\*\* corn is the vegetable with the highest lutein content tested (60% of total carotenoid content)  
\*\*\* orange pepper is the vegetable with the highest zeaxanthin content (37% of total carotenoid content)  
\*\*\*\* dark green leafy vegetables are high in lutein, but have only 0-3% zeaxanthin

while zeaxanthin concentrates closer to the fovea.<sup>28</sup> Some dietary lutein appears to be converted to a non-dietary form of zeaxanthin (meso-zeaxanthin). Infants have more lutein and less meso-zeaxanthin, leading to the speculation that they may not convert lutein as efficiently. Zeaxanthin appears to be preferentially taken up by cones, while lutein has an affinity for the rods.<sup>29</sup> See Table 1 for dietary sources of lutein and zeaxanthin.<sup>30</sup>

A multi-center study compared the serum levels of vitamins C and E, carotenoids, and selenium of 421 patients with neovascular AMD with levels of these same nutrients in 615 controls. Serum nutrients were classified as low, medium, or high. Persons with carotenoid levels in the medium and high groups demonstrated significantly reduced risk for neovascular AMD when compared to those with low serum carotenoids.<sup>31</sup> While no significant protection was found with vitamins C and E or selenium individually, an antioxidant index which combined these three with carotenoids showed dose-dependent significant reductions in risk.

An arm of the Eye Disease Case-Control Study conducted at five ophthalmology

centers in the United States examined dietary intakes of carotenoids, and vitamins A, C, and E in 356 subjects with advanced stages of AMD and 520 control subjects. Those in the highest quintile of carotenoid intake demonstrated a 43-percent lower risk for developing AMD compared with those in the lowest quintile. The carotenoids lutein and zeaxanthin were most closely correlated with a decreased risk.<sup>21</sup>

Low density of macular pigment, which permits blue light damage to the retina, represents a risk factor for the development of macular degeneration. The macular pigment also appears to protect the macula via antioxidant mechanisms. An evaluation of two subjects was conducted to determine if dietary supplementation with lutein (30 mg daily) for 140 days would increase macular pigment density.<sup>32</sup> Both subjects experienced an increase in optical pigment density, which began between 20 and 40 days after beginning lutein supplementation. The density increased an average of 1.13 +/-0.12 milliabsorbance units/day, resulting in a 39-percent increase in macular pigment density in one subject and a 21-percent increase in the second subject. The increased pigment density yielded a 30 to 40-percent decrease in blue light reaching the reti-

nal pigment epithelium, Bruch's membrane, and photoreceptors.

It is possible to impact the macular pigment density by dietary modifications as well. Thirteen subjects were fed either 60 g spinach and 150 g corn (n=10), 60 g spinach only (n=1), or 150 g corn only (n=2) for 15 weeks. Of the subjects who included spinach in their diet, eight subjects demonstrated an average 33-percent increase in serum lutein and 19-percent increase in macular pigment density; two showed a 31-percent increase in serum lutein but no change in pigment density; and one showed no changes in either serum carotenoids or pigment density. For the two subjects given corn only, one experienced a 70-percent increase in serum zeaxanthin and a 25-percent increase in macular pigment density.<sup>33</sup>

As mentioned above, smoking is a risk factor for macular degeneration. One study compared 34 smokers with 34 non-smokers and found the smokers had significantly reduced macular pigment density (0.16) compared to non-smokers (0.34); pigment density was inversely affected in a dose-dependent manner.<sup>34</sup> Previous studies have found smoking depresses serum carotenoid levels.<sup>35</sup>

There may be gender differences in macular degeneration risk, as some studies note an increased risk for females. The Beaver Dam study found women age 75 and older had a greater probability of developing neovascular AMD than men in the same age group.<sup>36</sup> The Eye Disease Case-Control Study found women with children were at higher risk than childless women.<sup>36</sup> If females are at higher risk, macular pigment density differences might play a role. A study from the Schepens Eye Research Institute in Boston found males had 38-percent higher macular pigment density than females, despite similar plasma carotenoid concentrations.<sup>37</sup>

### **Ginkgo and AMD**

A small double-blind trial compared

*Ginkgo biloba* with placebo in 10 patients with macular degeneration. In spite of the small population, statistically significant results in visual acuity were noted in the Ginkgo group.<sup>38</sup> The researchers speculated the effect was primarily due to Ginkgo's antioxidant effects.

### **Diabetic Retinopathy**

Retinopathy associated with diabetes can be particularly severe and is a leading cause of blindness in type 1 diabetes, but is also common in type 2 diabetes. The degree of retinopathy is closely associated with the duration of the diabetes, generally not occurring until ten years after disease onset.

### **Pathophysiology**

Two types of diabetic retinopathy have been identified: 1) non-proliferative or background retinopathy, characterized by increased capillary permeability, edema, hemorrhages, microaneurysms, and exudates, and 2) proliferative retinopathy, characterized by neovascularization extending from the retina to the vitreous, scarring, fibrous tissue formation, and potential for retinal detachment.<sup>1</sup>

There are numerous proposed mechanisms for the development of retinal changes in diabetes. One of the causes of diabetic complications, including retinopathy, is the development of glycosylated proteins—the attachment of sugars to proteins in the presence of high blood glucose.<sup>39</sup> Glycosylated proteins generate free radicals, resulting in oxidative tissue damage and depletion of glutathione. Glutathione has been found to be deficient in the retinas of diabetic dogs and rats.<sup>40</sup> Human diabetics with retinopathy have higher levels of malondialdehyde (a by-product of oxidative stress) when compared with diabetics without retinopathy and healthy controls.<sup>41</sup> Glycosylated proteins can themselves combine

with lipids and become damaged by free radicals, forming advanced glycated end products (AGE), which can deposit in blood vessels of the retina and contribute to neovascularization. There is evidence this process may be partially blocked by antioxidants.<sup>42</sup>

Type 1 diabetics have demonstrated decreased red blood cell fluidity and increased blood viscosity (which worsens with the stage of retinopathy).<sup>43</sup> These factors contribute to blood vessel blockage, decreased oxygenation of the retina, and the compensatory neovascularization seen in proliferative retinopathy. In the study cited above, reduced plasma selenium contributed to undesirable changes in blood viscosity.<sup>43</sup> Abnormal lipid profiles (high LDL and low HDL) seen in diabetes have been associated with decreased cell membrane fluidity in patients with diabetic retinopathy.<sup>44</sup>

Researchers disagree as to the extent of the effect of sorbitol accumulation on diabetic retinopathy. Aldose reductase-inhibiting drugs (which inhibit the conversion of glucose to sorbitol) have been studied both *in vitro* and in animals, with mixed results; some studies found no effect of these drugs on inhibition of retinopathy progression,<sup>45</sup> while other studies found involvement of sorbitol and benefit from aldose reductase inhibition.<sup>46</sup> However, because of the known involvement of sorbitol in the pathogenesis of diabetic cataracts, natural aldose reductase inhibitors such as quercetin, hesperidin, and naringin should be considered for diabetic patients. These will be discussed further in Part Two of this article.

Yet another controversy is whether elevated homocysteine levels contribute to diabetic retinopathy. A study reported in *The Lancet* examined 25 patients with diabetes, 12 with retinopathy and 13 without.<sup>47</sup> The patients with retinopathy all had abnormally high levels of homocysteine, while those without retinopathy did not. Another study examined 79 people with diabetes and 46 healthy controls and found no correlation between high

homocysteine levels and retinopathy, except in those patients who also suffered from nephropathy.<sup>48</sup> Because homocysteine can directly and indirectly damage vascular endothelial cells, it is entirely conceivable that it could damage blood vessels in the retina, contributing to retinopathy.

### **Blood Sugar Control**

Maintaining normal, or close to normal, blood glucose is key to preventing retinopathy. The Diabetes Control and Complications Trial studied 1,439 insulin-using diabetics with retinopathy.<sup>49</sup> The effect of standard insulin dosing (two daily injections) was compared to tighter control with frequent glucose testing and injections throughout the day. Although during the first few months of the study, tighter blood sugar control appeared to worsen retinopathy more than the conventional approach, better blood sugar control resulted in a significant decrease in long-term risk.

The United Kingdom Prospective Diabetes Study, the largest, longest-running study of people with type 2 diabetes, enrolled 5,200 participants and gathered data from 1977 to 1998.<sup>50</sup> The researchers found intense blood-sugar control with either insulin or oral sulfonylurea reduced the risk of retinopathy and nephropathy each by 25 percent. After examining the results, endocrinologist Alan Garber commented, "There is no limit to the benefit you can achieve when you lower blood sugars." While controlling blood sugar is vital to prevention of retinopathy, there are a number of nutrients and botanicals which may also be of benefit. For a summary, see Table 2.

### **Nutrients and Botanicals in the Prevention and Treatment of Diabetic Retinopathy**

**Table 2.** Nutrients and Botanicals for Prevention of Diabetic Retinopathy.

| Nutrient/Botanical     | Mechanism of Action                         |
|------------------------|---|
| Vitamin C              | antioxidant; prevents protein glycosylation |
| Vitamin E              | antioxidant; prevents protein glycosylation |
| Vaccinium myrtillus    | decrease capillary fragility                |
| Ginkgo biloba          | antioxidant                                 |
| OPCs                   | decrease capillary fragility                |
| Acetyl-L-carnitine     | antioxidant                                 |
| Magnesium              | correct a deficiency                        |
| Pyridoxal 5'-phosphate | correct a deficiency                        |

### Vitamin C

Several researchers have found vitamin C is lower in diabetics than non-diabetics, and lowest in those diabetics with retinopathy.<sup>51,52</sup> Potential mechanisms for vitamin C's prevention of retinopathy include free radical scavenging, prevention of protein glycosylation (shown in healthy humans and *in vitro*),<sup>53,54</sup> and decreasing capillary permeability<sup>55</sup> and fragility.<sup>56</sup>

### Vitamin E

Similar to the vitamin C findings, researchers have found lower vitamin E levels in diabetics than in healthy controls, and even lower levels in diabetics with retinopathy.<sup>52</sup> Some of the suspected mechanisms for ascorbate's benefit in retinopathy apply to vitamin E as well. For example, like vitamin C, vitamin E prevents both oxidative damage and protein glycosylation.<sup>53</sup> Both vitamin E and alpha-lipoic acid have been found to prevent oxidation of glycosylated proteins, further inhibiting damaging effects of glycosylation.<sup>57</sup> Animal studies have found glutathione levels to be low in diabetes; the depressed levels were restored with supplementation of vitamins C and E.<sup>40</sup>

Researchers have found an increase in activity of the enzymatic diacylglycerol protein kinase C (DAG-PKC) pathway in the retinas

of diabetic animals.<sup>58</sup> This increased enzyme activity appears to interfere with normal circulation to the retina. Vitamin E was found to normalize the activity of the DAG-PKC pathway, leading to improved retinal blood flow. Vitamin E also decreases platelet aggregation, providing another possible mechanism for improved retinal circulation in diabetes.<sup>59</sup>

### *Vaccinium myrtillus*

*Vaccinium myrtillus* (bilberry; see Figure 3) is being used widely for a wide array of ocular disorders, including diabetic retinopathy. Most investigations have focused on the flavonoid (anthocyanoside) content, which offers potent connective tissue stabilization,<sup>60</sup> decreased capillary fragility,<sup>61</sup> and antioxidant effects, and appears to have a particular affinity for the retina. Studies on bilberry for diabetic retinopathy have been very limited. An open trial of bilberry extract was conducted on 31 patients with retinal pathology from various causes; diabetic (n=20); retinitis pigmentosa (n=5); macular degeneration (n=4); and hemorrhagic retinopathy from anti-coagulant medications (n=2). Researchers reported a tendency toward reduced vascular permeability and incidence of hemorrhage in all patients, particularly those with diabetes.<sup>62</sup> Typical dosage is 80-160 mg three times daily of a standardized extract containing 25-percent anthocyanosides.



### **Ginkgo biloba**

*Ginkgo biloba* has been found, in animal experimentation, to have potential for treatment of retinopathy. Alloxan diabetic rats were administered electroretinograms, a measure of electric potentials in the retina in response to light stimuli; retinopathy decreases the amplitude of the electric potential.<sup>63</sup> Rats treated with Ginkgo demonstrated significantly greater amplitude after two months when compared with those on placebo. The effect was attributed to Ginkgo's antioxidant effects.

### **OPCs**

Oligomeric proanthocyanidins (OPCs) may also offer some protection from retinopathy by decreasing capillary fragility, much like anthocyanosides from bilberry. A small double-blind trial of 150 mg daily or placebo to a group of 25 subjects with diabetes and hypertension found OPCs decreased capillary fragility while there was no change in the placebo group.<sup>64</sup>

### **Acetyl-L-carnitine**

Acetyl-L-carnitine (ALC) compared to placebo normalized abnormal electroretinograms in diabetic rats; signs of improvement were increased b-wave amplitude and decreased latency of oscillatory potentials.<sup>65</sup> The mechanism for ALC's effect is unclear, but may be in part due to its antioxidant effects. ALC has also been found to decrease malondialdehyde content of nerve cells.<sup>66</sup>

### **Magnesium**

Diabetics appear to be deficient in magnesium and some researchers theorize this deficiency may contribute to retinopathy. Seventy-one insulin-dependent diabetics were divided into two groups depending on the severity of their retinopathy. While all subjects had some degree of magnesium deficiency, those with the most severe retinopathy demonstrated the most significant deficiency.<sup>67</sup>

### **Pyridoxine**

There may be a link between pyridoxine (B6) deficiency and diabetic retinopathy. A group of researchers gathered data over a period ranging from eight months to 28 years and noted an absence of retinopathy in those who supplemented B6.<sup>68</sup>

### **Retrolental Fibroplasia (Retinopathy of Prematurity)**

Retrolental fibroplasia is a major cause of vision impairment in premature infants. While it was more prevalent in the past, prior to an understanding of the effect of high oxygen concentrations on immature tissues in premature infants, it continues to be a cause for concern.

### **Pathophysiology**

Retrolental fibroplasia or retinopathy of prematurity (ROP) is a bilateral disorder characterized by neovascularization, primarily of the temporal regions of the retina. It is generally caused by exposure of the

**Figure 3.** *Vaccinium myrtillus*



infant's immature retinal vascular bed to high postnatal incubator oxygen concentrations. The condition occurs very rarely in premature infants not exposed to supplemental oxygen.<sup>1</sup> While it is known that immature retinal vessels are particularly sensitive to oxygen, the exact concentrations or duration of exposure necessary to instigate pathology is not known and probably varies considerably. It is known that the possibility of ocular damage may be present at oxygen concentrations above 30 percent. In severe cases the neovascularization invades the vitreous and may cause retinal detachment. In mild cases the vessel overgrowth resolves spontaneously. Other associated findings include glaucoma and myopia. Description of disease progression is by stage (see Table 3).

### Vitamin E

During the early to mid-1980s a number of studies on the use of vitamin E to prevent progression of ROP were conducted in several hospital settings. One such double-blind study examined 101 preterm infants given either 100 mg/kg/day or 5 mg/kg/day oral vitamin E. The researchers found a significant decrease in severity of retrolental fibroplasia in the group receiving large physiological doses of vitamin E (100 mg/kg/day) when compared to the group receiving low dose (5 mg/kg/day).<sup>69</sup> Continued evaluation by some of these same researchers examining three clinical trials of a total of 418 infants found that only continuous supplementation of vitamin E at high (adult doses) from the first hours of life suppressed the development of ROP.<sup>70</sup> Another study found oral dosing alone was as effective as a combination of oral dosing and IM injections.<sup>71</sup>

Another group of researchers reported on their findings of vitamin E in ROP in a

group of 191 preterm infants. Their analysis found three factors which distinguished infants who developed severe ROP from those who did not: 1) larger arterial PO<sub>2</sub> values, over 100 mm Hg; 2) lack of early vitamin E supplementation; 3) presence of intraventricular hemorrhage. They concluded with the recommendation that vitamin E be supplemented within the first 12 hours of life to all infants weighing less than 1500 g requiring supplementary oxygen.<sup>72</sup> Another study by these same researchers of 126 preterm infants supplemented with vitamin E found that none of the 99 surviving infants developed worse than stage 2 ROP, while three control infants were blinded in both eyes. They concluded that early administration of vitamin E did not affect the frequency of ROP, but significantly reduced its severity and subsequent eye damage.<sup>73</sup>

Studies to determine vitamin E's mechanism of action point to its effect on spindle cells. These cells are the embryonic precursors of inner retinal capillaries. Exten-

**Table 3.** Stages of Retinopathy of Prematurity.

Stage 1: demarcation line  
 Stage 2: intraretinal ridge  
 Stage 3: ridge plus extraretinal fibrovascular proliferation  
 Stage 5: total retinal detachment

sive increases in gap junctions between adjacent spindle cells appear to trigger neovascularization, dilation, and tortuosity of retinal vessels. Continuous vitamin E supplementation was able to preserve the embryonic state of the spindle cells in infants of 28 weeks gestation or older and transiently retard gap junction increases in infants of 27 weeks gestation or younger.<sup>74</sup>

Following this initial flurry of research,

the use of vitamin E to prevent progression of ROP appeared to be shelved while attention turned to treatment with laser, cryosurgery, and other high-tech procedures. In 1997 a group of researchers from the Department of Pediatrics at the University of Illinois dusted off the concept with a meta-analysis of previous research. The analysis of six trials examined 536 infants who were given therapeutic doses of vitamin E, and 551 controls. Although the incidence of ROP was similar in both groups (39.8 percent in the vitamin E group vs 43.5 percent in the control group), there was a 52-percent reduction in progression to stage 3 or higher ROP in the vitamin E group compared to controls.<sup>75</sup> The researchers recommended a re-evaluation of the use of vitamin E in reducing severe ROP. Since the current incidence of ROP in one retrospective study of 143 preterm infants was 2.2 percent for stage 1, 3.6 percent for stage 2, and 13 percent for stage 3 or higher,<sup>76</sup> it is apparent that current interventions are not preventing progression of this potentially devastating condition. Despite considerable evidence of the effectiveness of vitamin E in preventing progression of this condition, it is still considered “experimental” and has not become part of routine standard of care in prenatal units.

### **Other Associated Factors**

High serum iron levels caused by transfusions have been associated with an increased incidence of retinopathy of prematurity.<sup>77</sup> The investigators hypothesized the pro-oxidant effects of iron resulted in free radical damage.

A study assessed 253 infants in a critical care nursery at Georgetown University Medical Center to determine the association between systemic Candida and ROP. The researchers found systemic Candidiasis was an independent risk factor for stage 3 ROP; in addition, 41 percent (9/22) of infants with systemic Candida required laser surgery com-

pared to 9 percent (10/111) of infants without Candida.<sup>78</sup>

### **Vascular Retinopathies**

Vascular retinopathies are characterized by retinal hemorrhage, exudates, edema, ischemia, and infarct caused by ocular or systemic vascular disorders. Included are retinopathy of hypertension and retinopathy of arteriosclerosis. Treatment involves control of the primary underlying systemic disorder.

### **Retinitis Pigmentosa**

Retinitis pigmentosa (RP) is a slowly progressive, bilateral degeneration of the retina which can be either autosomal recessive, autosomal dominant, or X-linked. It also sometimes occurs as part of a syndrome complex.

### **Pathophysiology**

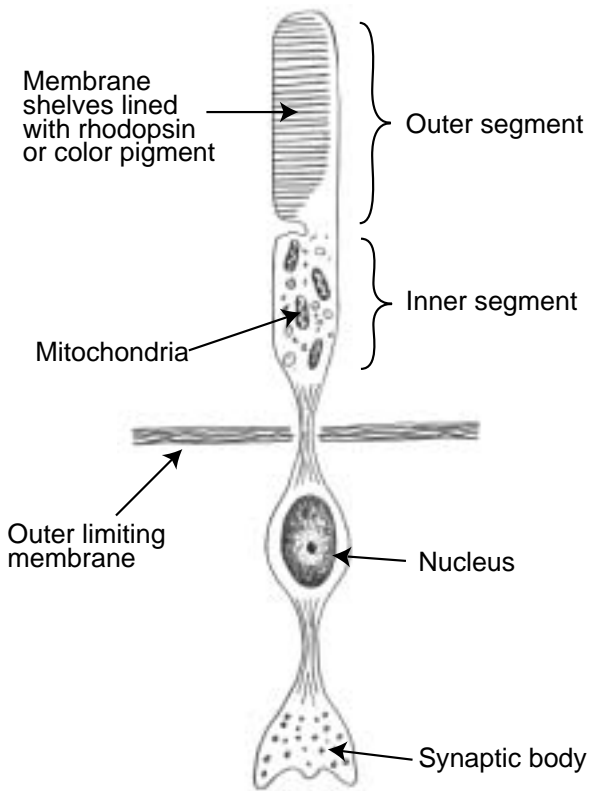
The retinal rods (see Figure 4) are affected most prominently, resulting in serious deterioration of night vision as early as childhood. As loss of vision progresses, peripheral vision deteriorates first, with a gradual increase in peripheral scotoma, resulting in tunnel vision and eventual complete loss of vision in some people. Other late manifestations can include macular degeneration, cataracts, and vitreous opacities.<sup>1</sup>

Impairment of the dopamine system may play a role in the pathophysiology of visual impairment in RP.<sup>79</sup> A decrease in cyclic GMP phosphodiesterase, resulting in accumulations of cGMP in photoreceptor outer segments, has also been implicated. This enzyme deficiency appears to involve a defect in retinoid metabolism.<sup>80</sup>

### **Taurine and Other Amino Acids**

Taurine is found in high concentrations in the retina of mammals. Taurine, which is necessary for normal vision, is released from the retina in response to light exposure and

**Figure 4.** Functional Components of the Rods and Cones.



actively transported by the retinal pigment epithelium to the choroid.<sup>81</sup> The effects of taurine-deficient diets on retinal degeneration in cats have been extensively examined. Cats provide a perfect laboratory for studying the effects of taurine deficiency because activity of enzymes such as cysteine sulfinate decarboxylase, necessary for the synthesis of taurine, is decreased.<sup>82</sup> Cats fed a casein diet deficient in taurine showed signs of retinal degeneration as measured by electroretinogram studies.<sup>83</sup> When the cats were fed diets supplemented with either taurine or its amino acid precursors, cysteine or methionine, only the taurine-supplemented group demonstrated improved ERGs,<sup>84</sup> further demonstration of cats' inability to synthesize taurine efficiently from its precursors.

Physiological changes in retinitis pigmentosa in humans resemble those of retinal degeneration in taurine-deficient cats,<sup>85</sup> and

a group of inherited, atrophic retinopathies occurring in dogs and cats also show marked similarities to the pathological findings seen in retinitis pigmentosa.<sup>86</sup> Serum levels of taurine do not appear to be a consistent marker for retinitis pigmentosa, however. While some researchers have found low serum levels in certain subgroups of people with RP,<sup>87</sup> other researchers have found no significant differences in levels between patients with RP and healthy controls.<sup>88,89</sup> Instead, patients with retinitis pigmentosa appear to have a deficiency of cellular uptake of taurine. One study found one-third less platelet uptake of taurine in patients with RP when compared to controls, suggesting RP is a disease which affects not only the eye but taurine transport and storage in general.<sup>90</sup> Another study found a decrease in both taurine and aspartate concentrations in platelets, but not in serum, of patients with RP, compared to controls.<sup>91</sup>

Amino acid profiles in general may be effected by retinitis pigmentosa. One study examined fasting whole blood levels of amino acids in 65 patients with RP and found eight with X-linked RP were deficient in both taurine and aspartate, 19 with autosomal recessive RP were deficient in threonine, and 10 with autosomal dominant RP were low in histidine.<sup>92</sup> Therefore, evaluation of amino acid status might be important when treating patients with RP.

### Vitamins A and E

While serum levels of vitamin A and beta carotene appear to be normal in patients with RP,<sup>93</sup> retinal pigment epithelium and rod photoreceptors appear to be deficient, indicating possible disturbed utilization of vitamin A or abnormalities in retinol binding protein in this population.<sup>94</sup> While a frank deficiency of vitamin A is not a cause of RP, vitamin A supplementation may be helpful for some patients with this condition. A large, double-blind trial of 601 patients (95 percent completed the

study) was conducted to assess the effects of vitamin A, vitamin E, and the combination in treating RP. Patients were randomly assigned to one of four groups: 1) 15,000 IU vitamin A daily, 2) 400 IU vitamin E daily, 3) 15,000 IU A/ 400 IU E daily, or 4) trace amounts of both (the control group). Visual acuity, visual field area, and electroretinograms were measured annually over a 4-6 year period. The two groups receiving vitamin A demonstrated a slower rate of decline in retinal function (measured by ERG). On the other hand, subjects in the vitamin E group demonstrated a more rapid decline in retinal function.<sup>95</sup> An *in vitro* study may explain this phenomenon. Vitamin E has been found to inhibit proliferation of retinal pigment epithelium in cell culture, which has positive implications for proliferative retinopathy (such as is seen in diabetes) but not for retinitis pigmentosa.<sup>96</sup>

Another smaller, shorter study did not conclude benefit from high-dose vitamin A supplementation. Forty-one patients with retinal pigment degeneration (27 with retinitis pigmentosa) were supplemented with 50,000 IU daily vitamin A for 28 days. Ten of these patients were also examined after 6 and 12 months. No significant changes in visual function were noted in either the short-term or relatively longer-term study evaluations.<sup>97</sup> It should be noted, however, that the positive study cited above was conducted over a 4-6 year period.<sup>95</sup> Long-term (12 years) supplementation of vitamin A in dosages of 15,000 IU daily to patients with RP (n=146) was found to yield no adverse side-effects.<sup>98</sup>

### **Other Potential Interventions for RP**

A study of 50 people aged 5-71 years was conducted using acupuncture to treat a variety of ocular conditions including myopia, glaucoma, retinitis pigmentosa, and optic nerve atrophy. Patients received one to three courses of 10-15 sessions each; points needled bilaterally in all patients included Extra 2, BL

2, GB 14 and 4, TH 17, and ST 1. Subjective improvement in visual acuity was observed in all patients. RP patients experienced an enlargement in the borders of the visual field measured by perimetry and isopter perimetry, as well as improved sensitivity to light differences measured by static perimetry.<sup>99</sup>

There is evidence that mitochondrial function in brain and skeletal muscle may be compromised in patients with RP. Coenzyme Q10 supplementation 100 mg/day to three patients with RP was found to improve brain energy reserve as measured by phosphocreatine in two patients and increase phosphocreatine synthesis in muscles of one patient who had been deficient prior to supplementation.<sup>100</sup>

Patients with night blindness, as seen in RP, may have faulty circadian rhythmic secretion of melatonin.<sup>101</sup> Supplementation with melatonin may be indicated in these patients. In addition, methylcobalamin may be a useful adjunct, as this active coenzyme form of vitamin B12 appears to be capable of enhancing light-sensitivity, modulating melatonin secretion, and normalizing circadian rhythms.<sup>102</sup>

### **Conclusions**

Over the past two decades, considerable preliminary research has pointed to the potential for dietary, supplemental nutrient, and botanical interventions in the prevention of serious ocular disorders of the retina. While much of the research on macular degeneration has been epidemiological, several small clinical studies have indicated benefit with nutrients such as zinc and botanicals such as Ginkgo. Nutrients or botanicals to consider for macular degeneration include carotenoids (particularly lutein and zeaxanthin), vitamins C and E, zinc, selenium, and *Ginkgo biloba*.

Diabetic retinopathy is best prevented by maintenance of good blood sugar control. However, research indicates vitamins B6, C, and E, magnesium, *Vaccinium myrtillus*,

*Ginkgo biloba*, acetyl-L-carnitine, and oligomeric proanthocyanadins (pine bark or grapeseed extract) may also help prevent or arrest this serious complication of diabetes.

Considerable evidence points to the benefit of immediate vitamin E supplementation to arrest the progression of retrolental fibroplasia caused by exposure of immature retinal vascular beds to high oxygen pressures. Although much of the research was conducted almost 20 years ago, supplementation of vitamin E to premature infants has not become routine in most hospital settings.

People with retinitis pigmentosa appear to have faulty utilization of both taurine and vitamin A. Supplementation of these two nutrients may improve outcomes in this condition. Other therapies to consider include acupuncture, CoQ10, melatonin, and methylcobalamin. High-dose vitamin E supplementation may be counter-productive. While there is considerable preliminary evidence of significant benefit from unconventional approaches to serious ocular disorders of the retina, extensive prospective clinical studies have not been conducted to evaluate most of these interventions. Since conventional medicine has focused primarily on interventions such as laser therapy, which is typically utilized after significant retinal pathology is evident, further research into preventive measures is warranted.

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