

INTEGRATED HEALTHCARE PRACTITIONERS

Integrated Healthcare Practitioners' Dietary and Nutritional Supplement, and Herbal Remedies Management Program

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SUCCESSFUL COMPLETION OF THE QUESTIONS AT THE END OF THIS PAPER HAS BEEN APPROVED FOR CONTINUING EDUCATION BY THE BDDT-N; 1.0 CREDIT NUTRITIONAL MEDICINE AND BY THE CNPBC; ONE CE HOUR.

Chronic Degenerative Eye Disease

Intervention with natural health products for prevention and treatment.

By Philip Rouchotas, MSc, ND

INTRODUCTION

Chronic retinal diseases include vascular retinopathies such as hypertensive retinopathy, diabetic retinopathy, central artery or vein occlusion, as well as non-vascular retinopathies such as age-related macular degeneration (AMD) (Merck 1999). In particular, AMD is the leading cause of blindness among individuals 50 years of age or older (Do 2009). AMD is estimated to affect approximately 1.75 million Americans over 40, while over seven million are estimated to be at high risk as assessed by the presence of drusen, or retinal deposits (Friedman 2004). Conventional therapy has long been limited primarily to laser photocoagulation; more recent pharmacotherapy has included anti-angiogenic agents such as ranibizumab, however intravitreal administration is invasive (Do 2009, Iu 2007, Merck 1999). As yet, there are no established treatments for the atrophic subtype of AMD (Iu 2007).

There are several natural health products (NHPs) with proven efficacy for AMD. A variety of these agents are discussed here. In addition, although the focus of this article will be AMD, these agents would also be appropriate for consideration in the treatment of related chronic diseases of the retina.

PATHOPHYSIOLOGY

There are two primary forms of AMD, atrophic (or "dry") AMD characterized by atrophic changes in the macular retinal pigment epithelium and degeneration of photoreceptors. Although the pathogenesis of atrophic

AMD is as yet unclear, it is thought that the collection and entrapment of cellular debris under the retina provokes a local inflammatory response leading to the accumulation of drusen (Iu 2007). Neovascular (or "wet") AMD is characterized by the formation of new blood vessels that grow from the choroids layer into or under the retina. Subsequent micro-hemorrhages and exudations from the fragile vessels develop into retinal edema and further degeneration (Iu 2007). Neovascular AMD requires an immediate referral to emergency services.

Risk factors include age and family history, hypertension, smoking, exposure to UV radiation, atherosclerotic vascular disease, diabetes, inflammatory disease, and obesity. These are thought to negatively affect choroidal circulation and contribute to oxidative insult of retinal pigment epithelium (Klein 2004).

NHPS OF INTEREST

NHPs with human evidence supporting use in degenerative eye conditions include: coenzyme Q10, fish oil/ DHA,

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Table 1. Current Evidence for Non Pro-vitamin A Carotenoids in AMD

Controlled Trials			
Lutein	Lutein 12 mg DHA 800 mg Lutein + DHA x 4 months	49 women were randomized to receive lutein, DHA, both, or placebo. In the lutein group, MPOD increased significantly at 3.0° (p<0.01). See Table 2 for DHA findings.	Johnson 2008
	Lutein 10 mg x 12 months	90 subjects with atrophic AMD were randomized to receive lutein, lutein + multivitamin and antioxidants, or placebo. MPOD increased significantly in the lutein group for patients with baseline MPOD ≤0.3 optical density units. This increase on MPOD translated into significant clinical improvements: in the lutein alone and lutein in combination groups, Snellen equivalent visual acuity improved 5.4 and 3.5 letters respectively. Contrast sensitivity, and subjective ratings of visual function also improved in both treatment groups, while there was no change in the placebo group.	Richer 2007 Richer 2004
Zeaxanthin (with or without lutein)	Zeaxanthin 1mg + Lutein 12mg x 6 months	108 subjects with and without AMD received 12 mg lutein + 1 mg zeaxanthin or no treatment. Those receiving lutein/zeaxanthin showed significant increases (+0.1 ODU) in MPOD in the retina, p<0.001 compared to control group.	Zeimer 2009 [Abst]
		Several additional human studies have also shown that lutein and/ or zeaxanthin ingestion increases MPOD.	Schalch 2007, Wenzel 2006
	20 mg total: Meso-zeaxanthin 14.9 mg, 5.5 mg of lutein, 1.4 mg of zeaxanthin x 120 days	19 subjects were randomized to meso-zeaxanthin supplement or placebo. Supplemented subjects showed significant increases in MPOD compared to placebo, 0.59 versus -0.17 milli-absorbance unit/day	Bone 2007
	Zinc 22.5 mg, Copper 1mg, Lutein 10mg, Zeaxanthin 1mg, Astaxanthin 4mg, VitE 30 mg, VitC 180 mg.	27 subjects with early AMD and visual acuity ≥0.2 logarithm of the minimum angle of resolution were randomized to receive supplementation with vitamin C, vitamin E, zinc, copper, lutein, zeaxanthin, and astaxanthin or no treatment. After 6 and 12 months, eyes in the treatment group showed highly significant increases in multifocal electroretinogram response amplitude densities in an area near the fovea (P<0.01), whereas no significant change was observed in the control group.	Parisi 2008

Ginkgo biloba, melatonin, Vaccinium, zinc, and non-provitamin A carotenoids such as lutein and zeaxanthin. Of these, the perhaps best known and most studied are the carotenoids. These NHPs are discussed here in sequence.

NON PROVITAMIN A CAROTENOIDS

The xanthophylls lutein (L) and zeaxanthin (Z) are the main constituents of the yellow macular pigment that accumulates in its highest density in the macula lutea, or “yellow spot,” of the fovea. The macula lutea possesses the highest concentration of these xanthophylls in the human body, and it is thought that they act as antioxidants to blue light exposure there (Schalch 2007).

Observational evidence has found an inverse association between intake of carotenoids, specifically lutein and zeaxanthin, and risk of AMD. Eyes of individuals with AMD have been found to have significantly lower

levels of lutein and zeaxanthin than those of non-AMD controls, with up to 62% lower levels in the macula (Bone 2001). A prospective cohort study by Delcourt et al found that those with the highest quintile of plasma zeaxanthin had significantly lower risk of age related maculopathy (OR=0.07; 95% CI: 0.01-0.58) (2006). Gale et al found protective effects from higher levels of zeaxanthin but not lutein, and have suggested that zeaxanthin may be more relevant for AMD than lutein (2003). Lutein remains the carotenoid most well studied for AMD in clinical trials, however.

The LUXEA (LUtein Xanthophyll Eye Accumulation) study was a randomized placebo-controlled study investigating the comparative effects of lutein, zeaxanthin, or both on macular pigment optical density (MPOD) in the fovea and parafovea. Daily doses of 10 and 20mg/d of either carotenoid or both were used over a

two to six month period (Schalch 2007). Lutein alone or lutein plus zeaxanthin increase MPOD 15% compared to placebo. Supplementation of zeaxanthin alone produced similar pigment accumulation in both fovea and parafovea, indicating that while lutein is predominantly deposited in the fovea, zeaxanthin deposition appears to cover a wider retinal area. An estimated 14% MPOD increase was seen with zeaxanthin alone (Schalch 2007).

Several additional human studies have confirmed the ability of carotenoids to increase MPOD; one study correlated this with improved ability of the retina to sense red-green light (Rodriguez-Carmona 2006).

COENZYME Q10

Coenzyme Q10 or ubiquinone is a physiologically important lipophilic antioxidant and neuroprotectant, and an essential component in mitochondrial function, including regulation of mitochondrial permeability and ATP generation. Glutamate has been implicated in mediating free radical damage and excitotoxic neuronal death, and CoQ10 has been shown to reduce increases in extracellular glutamate induced by retinal ischemia (Russo 2008). Retinal CoQ10 content decreases by up to 40% between the ages of 30 and 80 years (Qu 2009), and serum CoQ10 levels have also been found to be decreased in patients with AMD compared to controls (Blasi 2001). Supplementation with CoQ10 in combination with L-carnitine and omega-3 fatty acids, other promoters of mitochondrial ATP production and lipophilic antioxidants, has been shown to improve visual function in AMD (Feher 2005).

FISH OIL/DHA

Docosahexaenoic acid (DHA) is a key fatty acid found in the retina; rod outer segments in particular have a high DHA content and must be routinely shed and replaced. In addition to its function as a structural component in the neuronal cell (retinal cell) membrane, DHA (and EPA) increase plasma HDL-C concentrations. HDL-C is a transporter of lutein and other xanthophylls to the retina, and thus increasing HDL via fish oil supplementation augments the effect of lutein on AMD (Johnson 2008).

Supplementation with DHA has been shown to improve AMD (secondary prevention), and a recent meta-analysis pooling data from both human trials and observation evidence found significant benefits from regular fish intake for primary prevention of AMD. High dietary intake of omega-3 fatty acids was associated with a 38% reduction in the risk of late AMD (OR 0.62; 95% confidence interval, 0.48-0.82), while fish intake at least twice a week was associated with a reduced risk of both

early AMD (OR, 0.76; 95% CI, 0.64-0.90) and late AMD (OR, 0.67; 95% CI, 0.53-0.85) (Chong 2008).

In addition, supplementation with DHA has been shown to improve retinal function in infants, particularly preterm infants. Approximately 83mg DHA per day improved tests of retinal maturity in breast fed six month olds when given for six months; this was presumably due to inadequate delivery in breastmilk, since control infants had a sharp decline in serum DHA over the study period (Hoffman 2004a). Other studies have found a positive relationship between infant DHA status and retinal maturity at birth in infants born to mother supplemented with DHA (Malcolm 2003).

MELATONIN

Melatonin is a neurohormone with potent antioxidant activity, and is naturally synthesized in the retina. Melatonin functions in many capacities within the eye: control of retinomotor movement, rod outer segment shedding, phagocytosis, protection of retinal pigment oxidative damage, and regulation of intraocular pressure (Lundmark 2006). As a lipophilic antioxidant with a natural affinity for the retina, melatonin is thought to protect photoreceptor membranes from oxidation. Melatonin production is known to decrease with age, leaving the aged retina much more susceptible to oxidative damage of the retina, and supplementation has been shown to improve AMD in humans (Lundmark 2006, Yi 2005).

ANTHOCYANINS, GINKGO

Vaccinium species and Ribes nigrum contain high levels of anthocyanidins, potent antioxidants that are thought to increase regeneration of rhodopsin, stabilize collagen fibers, promote collagen biosynthesis, decrease capillary permeability and fragility, and inhibit platelet aggregation and edema (Nakaishi 2000, Vaccinium myrtillus 2001). Although there is no human evidence available on Pubmed for Vaccinium in retinopathies, Mills and Bone cite two Italian randomized, placebo controlled trials using 115mg bilberry anthocyanins for 1 and 12 months, respectively, in patients with early stage retinopathy secondary to either diabetes or hypertension. These trials found “reduction of hard exudate” and “significant improvements in the ophthalmoscopic and angiographic patterns in 77-90% of treated patients” (Mills 2000).

Ginkgo improves microcirculation to the retina, and thereby improves tissue oxygenation and clearance of potentially damaging substances and mediators. Ginkgo should not be given to patients with blood clotting disorder, hemorrhagic conditions, or on anticoagulation therapy (see Table 2).

Table 2. NHPs for Macular Degeneration and Other Retinopathies: Controlled Trials

Ingredient	Daily Dose	Evidence	References
Coenzyme Q10	2 caps containing CoQ10 10mg, omega-3 fatty acids 530mg, and L-carnitine 100mg x 12 months	106 patients with early AMD were randomized to combination treatment or placebo. After 12 months, there were significant improvements in visual field mean defect (VFMD), visual acuity, foveal sensitivity, and fundus alterations in the treated group. 2% the treated group vs 17% of controls showed clinically significant (>2.0 dB) worsening in VFMD (odds ratio: 10.93). Drusen-covered area of treated eyes decreased significantly in the treatment group, but increased in controls, suggesting treatment related reabsorption of drusen.	Feher 2005
Fish oil/ DHA	See Table 1. Lutein 12mg DHA 800mg Lutein + DHA x 4 months	49 women were randomized to receive lutein, DHA, both, or placebo. DHA increased MPOD at 0.4° (P<0.05), showing that while that lutein increased pigmentation density eccentrically, DHA increased pigmentation centrally within the retina.	Johnson 2008
	DHA 400mg x 4 years	44 patients with retinitis pigmentosa were randomized to DHA or placebo. Although there was no difference between groups in cone function, there was significantly less change in fundus appearance in the DHA group (P=0.04) after 4 years. In subset analysis, DHA reduced rod electroretinogram (ERG) functional loss in patients aged <12 years (P=.040) and preserved cone ERG function in patients ≥12 years (P =0.038).	Hoffman 2004 b
	Combination of VitA 10,000 IU carotene 18,000 IU VitC 452mg VitE 200 IU Zinc 69.6mg Copper 1.6mg Taurine 400 mg EPA 180mg DHA 120mg Lutein 8mg Zeaxanthin 400mcg	Prospective Cohort Study 37 subjects with dry AMD receiving the supplement were compared to control subjects constructed from the literature who had been given "400 mg vitamin C, 200 IU vitamin E, 40 mg zinc, and 3,000 IU beta-carotene". 76.7% of subjects receiving the nutritional supplement demonstrated stabilization or improvement of best corrected visual acuity at 6 months. Visual acuity improved significantly compared to baseline (p=0.045).	Cangemi 2007
Ginkgo biloba (Ginkgo)	60 or 240mg/d Ginkgo extract Egb 761 x 24 weeks	99 subjects with dry AMD and impaired vision were given one of two doses of Ginkgo extract for 24 weeks. Marked improvement in visual acuity was reported, beginning at 4 weeks and continuing until 24 weeks. The number of subjects with acuity improvements ≥0.2 in the high dose group was nearly double that in the low dose group. No serious adverse events were reported.	Fies 2002 [Abst]
	Not specified	10 patients with AMD were given Ginkgo or placebo. A significant improvement in long-distance acuity was seen in patients receiving Ginkgo.	Lebuisson 1986 [Abst]
	Dose not specified; duration 6 months	29 subjects with early diabetic retinopathy evidenced by angiography, and associated with a blue-yellow dyschromatopsia were given Ginkgo or placebo. At 6 months, there was a tendency toward improvement in study measures of color vision in the Ginkgo group, while there was worsening in the placebo group. The difference between groups was significant in subjects without retinal ischemia.	Lanthony 1988 [Abst]

Table 2 continued

Melatonin	3mg at bedtime x at least 3 months	Uncontrolled trial 100 subjects diagnosed with wet or dry AMD were given melatonin in a prospective study. At 6 months, visual acuity had been kept stable, a better result than the otherwise estimated natural course. Over entire the study period, marked improvements compared to baseline were seen with respect to pathological changes on funduscopy.	Yi 2005
Ribes nigrum (Black currant)	12.5-, 20-, or 50mg Black Currant Anthocyanoside (BCA) extract as a single dose	Study on Ribes for Visual Fatigue 21 subjects confirmed to be free of eye disease were given one of 3 doses of BCA extract, or placebo, as a single dose. At the 50mg dose, there was a significant lowering of the dark adaptation threshold (P=0.011). Ribes promoted recovery from or prevented work-induced refractive alteration (a measure of visual fatigue), and significantly improved subjective symptoms of visual fatigue.	Nakaishi 2000
Vaccinium myrtillus (Bilberry)	50-120mg of anthocyanins, ~20- 50g of fresh fruit	No human trials of Vaccinium for AMD or other retinopathies were found in pubmed. Mills and Bone cite two Italian randomized, placebo controlled trials demonstrating benefit in diabetic and/ or hypertensive retinopathy. See text.	Mills 2000
Zinc	50mg zinc- monocysteine (ZMC) x 6 months (Both groups given a multivitamin)	40 subjects with AMD, loss of visual acuity, macular drusen (hyaline deposits under the retina), and pigment changes were given zinc or placebo. At 6 months, the ZMC group showed improved visual acuity (P<0.0001) and contrast sensitivity (P<0.0001). Macular light flash recovery time shortened in the ZMC group by 7.2 seconds (left eye) to 7.4 seconds (right eye, P<0.0001 for both).	Newsome 2008
	200mg zinc sulfate x 2 years	151 subjects with drusen (retinal deposits) or macular degeneration were randomized to zinc or placebo. After 12 and 24 months, the zinc group had significantly less visual loss compared to the placebo group.	Newsome 1988

COMBINATIONAL ANTIOXIDANTS

The Age Related Eye Disease Study (AREDS) was a randomized controlled trial examining the effect of a combination of antioxidants in 3,640 patients with AMD. Subjects were assigned to receive one of four treatments: (1) antioxidants (vitamin C 500mg; vitamin E 400 IU; and beta carotene 15mg); (2) zinc, 80mg as zinc oxide and copper, 2mg as cupric oxide; (3) antioxidants plus zinc; or (4) placebo for an average 6.3 years. Analysis showed significant odds reduction for the development of advanced AMD with antioxidants plus zinc (OR 0.72; 99% CI 0.52-0.98). The ORs for zinc alone and antioxidants alone were non-significantly reduced: 0.75 (99% CI, 0.55-1.03) and 0.80 (99% CI, 0.59-1.09), respectively. Both zinc alone and antioxidants plus zinc significantly reduced the odds of developing advanced AMD in higher-risk subjects, however. Only antioxidants plus zinc significantly reduced rates of moderate visual acuity loss (OR, 0.73; 99% CI, 0.54-0.99) (Age Related Eye Diseases Study Group 2001).

ZINC

Zinc is thought to protect the retina via antioxidant activity, enhancement of connective tissue synthesis, and through its effect as a cofactor for enzymes in the chorioretinal complex. The retina contains the highest

concentrations of zinc in the body in women, and is second to prostate content in men. Zinc has been found effective for dry AMD both in combination with other antioxidants (AREDS Study) and independently. Both Newsome (1988) and AREDS also found trends to lower incidence of wet AMD with zinc supplementation.

Despite its impressive efficacy results, safety concerns exist around long-term supplementation with zinc. Upon secondary analysis, the AREDS group found increased rates of genitourinary tract complications among zinc-supplemented subjects (Johnson 2007). 11.1% of zinc supplemented participants versus 7.6% of non-zinc supplemented participants (P=0.0003). Elevated risk was most evident in men (RR 1.26, 95% CI 1.07-1.50, P=0.008). The most common presentations included benign prostatic hyperplasia/urinary retention (benign prostatic hyperplasia), urinary tract infection, urinary lithiasis and renal failure. Increased risk of urinary tract infection was the most significant finding among women (2.3% vs 0.4%, RR 5.77, 95% CI 1.30-25.66, P=0.013).

CONCLUSION

AMD is a chronic degenerative disease of the retina mediated by oxidative damage and local inflammatory changes. While pharmaceutical treatment of AMD

remains limited, several natural substances exist with human evidence of benefit in the treatment and prevention of this condition. These include lutein and other non-provitamin A carotenoids, coenzyme Q10, DHA, Ginkgo, melatonin, Vaccinium, and zinc.

Long-term administration of supplemental zinc needs to be weighed against possible detrimental impact from the intervention. Given the impressive efficacy and safety profile of other strategies reviewed, the risk profile of zinc need be considered prior to recommending its use. ■

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Questions

1. Choose the correct statement concerning the pathophysiology of AMD.
 - A) Fundoscopic observation of wet AMD (elevated macula, scarring under the macula, retinal detachment, macular edema, hemorrhage) is a cause for immediate referral to an emergency department.
 - B) Fundoscopic observation of dry AMD (yellow spots-drusen, retinal pigmentation changes, chorioretinal atrophy) is a cause for immediate referral to an emergency department.
 - C) Wet AMD is characterized by atrophic changes in the macular retinal pigment epithelium and degeneration of photoreceptors.
 - D) Dry AMD is characterized by the formation of new blood vessels that grow from the choroids layer into or under the retinal.

2. Choose the most appropriate selection of AMD risk factors from the options presented below.
 - A) Family history, survivor of hormone- dependant cancer, comorbidity of irritable bowel syndrome.
 - B) Hypertension, previous history of undergoing revascularization surgery, diabetes.
 - C) Vegetarian dietary pattern, participant in elite level physical training, fruit and vegetable- based diet.
 - D) History of depression comorbid with ADHD, recent history of divorce, under 40 years of age.

3. Concerning controlled human clinical intervention trials, select the option below best supported for management of AMD.
 - A) Beta carotene
 - B) Lycopene
 - C) Zeaxanthin
 - D) Lutein

4. Concerning CoEnzyme Q10 in AMD management?
 - A) Several controlled human studies have demonstrated efficacy of CoQ10 at 100mg per day for delaying progression of, and reversing established, AMD.
 - B) No human studies to date have examined the ability of CoQ10 to impact the course of AMD, although studies in animals are impressive.
 - C) One human study has combined CoQ10 with L- carnitine and fish oil, revealing positive results of an impressive magnitude.
 - D) CoQ10 acts as an important structural component of retinal cell membranes, thereby improving AMD outcomes upon supplementation.

5. DHA has reproducibly demonstrated efficacy in improving outcomes associated with AMD management. Suggest the most appropriate mechanistic basis upon which DHA delivers such outcomes.
 - A) Important structural component of retinal membranes.
 - B) Delivers anti inflammatory effect through metabolism to new species of cytokines, relative to arachidonic acid.
 - C) Increases HDL-C, an important carrier for lutein and other carotenoids.
 - D) All of the above contribute to the mechanisms by which DHA impacts degenerative eye disease.

6. Lutein and zeaxanthin accumulate in the macula lutea of the fovea of the eye. Observational evidence has demonstrated that concentrations of lutein and zeaxanthin decline with age.
 - A) True
 - B) False

7. Zinc has demonstrated evidence of concern, specifically with respect to increased risk of hospital admissions for genitourinary complications in older men and women.
 - A) True
 - B) False

8. Zinc supplementation in older women has been associated with increased risk of urinary tract infection.
 - A) True
 - B) False

9. Given demonstration in controlled human studies of efficacy for degenerative eye disease using melatonin, lutein, zeaxanthin, CoEnzyme Q10, and bilberry, it appears reasonable to propose oxidant stress is a major contributor to the pathogenesis of AMD.
 - A) True
 - B) False

- 10) Diabetic individuals are at increased risk of AMD, and also at high risk for diabetic retinopathy. A prescription for increased berry consumption among diabetic individuals, and/ or administration of a blend of non provitamin A carotenoids and berry extracts, is an appropriate strategy for prevention of future degenerative eye complications in these high risk individuals.
 - A) True
 - B) False

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