Nutrition and Behavior as it Applies to Systemic and Ocular Disease 2009

Specific Nutrients and Their Relevance to Disease

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Constituents of a Diet that Support Healthy Systemic and Ocular Function

Vitamin C

Linus Pauling brought Vitamin C to the forefront of healthcare by advocating mega-doses of Vitamin C to fight colds and minimize the risk of cancer. Even recently studies continue to corroborate his presumptions. The new information relates that the group most prone to enjoy the benefits of Vitamin C for the common cold are those individuals under heavy short-term physical stress. [280] Vitamin C is a water-soluble antioxidant working in concert with Vitamin E. Vitamin C must be obtained from the diet with absence creating the disease, scurvy. Early symptoms of scurvy include fatigue resulting from lowered levels of carnitine and norepinephrine.[281]

Vitamin C (Ascorbic Acid) is required for collagen synthesis, the synthesis of norepinephrine, carnitine and the conversion of cholesterol to bile acids. The overwhelming fame of Vitamin C is associated with its role as an antioxidant for the protection of molecules from damage by free radicals and reactive oxygen species (ROS) created during metabolism and toxin exposure such as smoking which creates oxidative stress.

IOP can be reduced by increasing concentrations of absorbate in the aqueous humor. This can be done by supplementing with vitamin C (0.5 gm/kg body weight). The IOP-lowering actions of vitamin C occur by improving collagen formation, increasing blood osmolarity, improving aqueous outflow, inhibiting lipid peroxidation and raising glutathione levels.[282-284] Vitamin C is known as a very active antioxidant that also creates an increase in Immunoglobulin A (IgA) and Immunoglobulin M (IgM) within the framework of the immune system.

There is the suggestion that vitamin supplementation suppresses leukocyte adhesion and thus endothelial dysfunction, associated with increase in iris blood flow perfusion in diabetes. It has also been suggested that the antioxidant vitamin C may be a therapeutic agent for preventing diabetic retinopathy. [285] Diabetes mellitus is associated with increased oxidative stress. One study suggests that supplementation with antioxidant vitamins C and E probably plays an important role in improving the constitution of the ocular surface in the patient with diabetes.[286] Plasma vitamin C levels are inversely associated with the risk for type 2 diabetes. There is an inverse association between fruit and vegetable intake and the risk for type 2 diabetes, with a greater effect for fruit intake.[287] Regarding Vitamin C as a part of an anti-Age Related Macular Degeneration formula, it has been shown that blue light could induce DNA damage to RPE cells but vitamin C could protect the RPE cells from the blue light-induced DNA damage.[288] Regarding anterior segment, the addition of ascorbic acid to the irrigation solution reduced the amount of endothelial cell loss during phacoemulsification by approximately 70%.[289] Likewise a significantly reduced mean level of ascorbic acid was observed in the aqueous humor of patients with exfoliation syndrome in one study. In view of the fact that ascorbic acid is a major protective factor against free radical action, a role for free radical action is suggested as a possible factor in the genesis of exfoliation syndrome.[290]

The utilization of Vitamin C for the prevention of cataract has long been in the literature. While studies continue to be controversial one

study showed the risk for cataract is 60% lower among persons who use multivitamins or any supplement containing vitamin C or E for more than 10 years. However the use of vitamins for shorter duration is not associated with reduced risk for cataract.[291] Another study demonstrated that Vitamin C reduced the risk of cortical cataracts in women aged 60 years or less and carotenoids reduce the risk of posterior subcapsular cataract in women who have never smoked.[292] Research by the Nutrition and Vision Project (NVP), a cooperative effort of Harvard and Tufts University scientists, has found that women who consume higher-than-recommended doses of vitamin C may lower their risk for more than one type of cataract.[293]

Immune system activities of Vitamin C are extensive. Vitamin C enhances prostaglandin E1 (PGE1) and thus assists in the regulation of T cell function. Vitamin C increases killer T cell activity and B cell function. It also increases glutathione levels. It is known to protect against viruses by strengthening connective tissue and neutralizing toxins released by phagocytes. The RDA for Vitamin C is 100 to 125 mg/day. The tolerable upper level for vitamin C is established at 2000 mg/day. [294] Daily supplementation of vitamin C is recommended with consideration for the increased risk for kidney stones. [295] Recommended levels vary considerably with the sources and care should be exercised when evaluating these variables.

Potential harms of all variations of high-dose antioxidant supplementation must be considered. These may include an increased risk of lung cancer in smokers (beta-carotene), kidney stones, heart failure in people with vascular disease or diabetes (vitamin E) and hospitalization for genitourinary conditions (zinc).

Vitamin D

Vitamin D is a fat-soluble vitamin (in actual fact a steroid hormone) essential for promoting calcium absorption in the gut and maintaining adequate serum calcium and phosphate concentrations to enable normal mineralization of bone and to prevent hypocalcemic tetany. It is also needed for bone growth and bone remodeling.[296] Severe Vitamin D deficiency in infants and children results in rickets with growth plate enlarging without the support of mineralization of the long bones. This results in bowing. Vitamin D3 (cholecalciferol) can be synthesized by humans in the skin upon exposure to ultraviolet-B (UVB) radiation. It can also be obtained from the diet, but is fat-soluble. Sufficient vitamin D prevents rickets in children and osteomalacia in adults and, together with calcium, vitamin D helps protect older adults from osteoporosis. A quantitative meta-analysis recently concluded that at a mean daily dose of vitamin D of 528 IU there was a significant decrease in death (7% to 8%) for those using vitamin D supplement. [297]

It has been estimated that 50% to 60% of people do not have satisfactory vitamin-D status, likely related to urbanization, demographic shifts, decreased outdoor activity, air pollution and global dimming, as well as decreases in the cutaneous production of vitamin D with age. One prospective cohort study demonstrates for the first time that low 25-hydroxyvitamin-D and 1,25-dihydroxyvitamin-D levels are associated with increased risk in all-cause and cardiovascular mortality compared with patients with higher serum vitamin-D levels.[298-300] Another recent study found that 40.7% of patients with chronic migraine were deficient in 25-hydroxyvitamin D. The study also showed that the longer individuals had chronic migraine, the more likely they were to be vitamin D deficient. [301]

Vitamin D deficiency is widespread among patients being treated for osteoporosis, and such deficiency should be treated aggressively.[302] Recent reports have increased the awareness of a much broader role for vitamin D. Vitamin D is involved in differentiation of tissues during development and in proper functioning of the immune system. Over 900 different genes are now known to be able to bind the vitamin D receptor, through which vitamin D mediates its effects. The majority of effects of vitamin D in the body are related to the activity of 1,25(OH)2D including 50 specific genes. 1,25(OH)2D also inhibits proliferation and stimulates differentiation of cells as well as having activity as an immune

system modulator. It is even suggested that 1,25(OH)2D may enhance innate immunity and protect against many autoimmune disorders.[303-304] Evidence also continues to accumulate suggesting a beneficial role for vitamin D in protecting against autoimmune diseases, including multiple sclerosis and type I diabetes, as well as some forms of cancer, particularly colorectal and breast.[305-306] Most biological effects of Vitamin D are mediated through a nuclear transcription factor VDR.[307-309] A recent article concludes that there is ample biological evidence to suggest an important role for vitamin D in brain development and function, and that supplementation for groups chronically low in vitamin D is warranted. Since Calcium is so linked to neurodegeneration, one may hypothesize a link between Vitamin D, the immune system and the negative actions of the calcium ion.[310]

Hypovitaminosis D, especially at levels less than 30 ng/mL, is associated with an increased risk for Myocardial Infarct in men. Vitamin D is likely to exert its effect on the risk for cardiovascular disease via vascular smooth muscle cell proliferation, inflammation, vascular calcification, the renin-angiotensin system, and blood pressure.[311-312] The rate of cardiovascular disease–related deaths is greater at higher latitudes, lower at higher altitudes, and higher in the winter months — all associations related to vitamin D deficiency. The vitamin D axis affects vascular smooth muscle cell proliferation, inflammation, vascular calcification, the renin-angiotensin system, and blood pressure, all of which affect cardiovascular disease and MI risk, but evidence linking hypovitaminosis D and MI is sparse. Current recommendations for vitamin D are 200 to 600 IU per day, which may be inadequate to prevent cardiovascular disease. Another recent study demonstrated that use of calcitriol in patients with stage III or IV Chronic Kidney Disease (CKD) with hyperparathyroidism is associated with reduced risk for mortality and long-term dialysis and that the use of calcitriol in patients with stage III or IV CKD with hyperparathyroidism is associated with increased risk for hypercalcemia. CKD affects more than 10% of the US population with disturbances in vitamin D and mineral metabolism. [313]

For the first time Vitamin D deficiency has been linked to a poorer outcome in breast cancer.[314] Risk factors for Vitamin D deficiency include: dark skin, sunscreens, clothing covering the majority of the skin, increasing age, gastrointestinal disorders associated with fat malabsorption, obesity, bariatric surgery, ill-advised dieting, and a poor diet. The results of most clinical trials suggest that vitamin D supplementation can slow bone density losses or decrease the risk of osteoporotic fracture in men and women.[315-318] but the issue is still very controversial. Indeed, vitamin D3 (cholecalciferol) is now known to be greater than three times more potent than vitamin D2.[319-320] In order for vitamin D supplementation to be effective in preserving bone health, adequate dietary calcium (1,000 to 1,200 mg/day) should also be consumed. In general adults should take a supplement that supplies 400IU of vitamin D3 daily and should have 10-15 minutes of sun exposure at least three times a week as close to noon as possible. Should sunlight exposure be unattainable, 800IU of D3 is advised. In reality it is best to aim for serum levels of 80 nmol/L to minimize risk of disease. Toxicity-hypercalcemia can lead to bone loss, kidney stones, and calcification of the heart and kidneys. Because the consequences of hypervitaminosis D and ensuing hypercalcemia are severe, the Food and Nutrition Board established a very conservative upper limit of 2,000 IU/day (50 mcg/day) for children and adults 321 while other reports suggest 10,000IU is tolerated.[322-323]

A recent study, while equating low vitamin D levels to an increased risk of mortality, concludes that they would not advise people to take supplements without knowing their vitamin-D levels and that the most sensible advice for those wanting to ensure their levels remain optimal is to spend 10 to 15 minutes per day in the sun and to eat vitamin-D-fortified foods, such as milk and oily fish.[324]

More recent studies relate the importance of Vitamin D3 to the eyes. Based on encouraging preliminary findings, more study is recommended on the benefit of antioxidant supplements for age-related macular degeneration and of selenium for cancer prevention. In contrast to the state of the art for antioxidant supplements, there is strong and

compelling support for the health benefits of supplements of Vitamin D and calcium when intake/status of these nutrients is not optimal. Thus, specific recommendations for these supplements in older adults are warranted. [325] It has been shown that Levels of serum vitamin D were inversely associated with early AMD but not advanced AMD and that milk intake was inversely associated with early AMD. Coincidently fish intake was inversely associated with advanced AMD in this report. It was reported that consistent use vs nonuse of vitamin D from supplements was inversely associated with early AMD only in individuals who did not consume milk daily.[326] Carrying this one step further, it was found that Higher levels of Bone Mineral Density (BMD) may be associated with lower risk for ARM. The underlying mechanism is unknown, although BMD may be a marker for lifetime endogenous estrogen exposure.[327]

Vitamin D is present in only a few foods (e.g. fatty fish), and is also added to fortified milk, but our supply typically comes mostly from exposure to ultraviolet rays (UV) in sunlight. UV from the sun converts a biochemical in the skin to vitamin D, which is then metabolized to calcitriol, its active form and an important hormone. Formation of vitamin D by UV can be 6 times more efficient in light skin than dark skin, which is an important cause of the known widespread vitamin D deficiency among African Americans living in northern latitudes. The issue of how Vitamin D relates to the general and ocular health of individuals is evolving with research outstripping one's ability to "keep up." A recent AARP magazine presented the following as cited by Michael F. Holick PhD, MD of the Vitamin D, Skin and Bone Research Laboratory of Boston University Medical Center.

"To get the vitamin D value of ten minutes' exposure to sunlight, you'd have to eat… 6 ½ pounds of shitake mushrooms or 150 egg yolks or 3 ¾ pounds of fresh farmed salmon or 30 servings of fortified cereal or 2 1/6 pounds of sardines or 30 cups of fortified orange juice." Do the calorie count on that exercise and realize that food sources of vitamin D actually complicate the issue.

Vitamin E

Alpha-tocopherol is the only form of Vitamin E in the human body and is the form recommended for supplementation. Vitamin E is the body's primary fat-soluble antioxidant and it must be obtained from food or supplements. As an antioxidant Alpha-tocopherol neutralizes free radicals then must be transformed back to Alpha-tocopherol with the assistance of other antioxidants such as Vitamin C. Vitamin E travels through the body in low-density liporoteins which protect them from from oxidation. Vitamin E is known to affect the expression and activity of immune and inflammatory cells, to enhance vasodilation and to inhibit the activity of the cell signaling molecule protein kinase C (PKC). Modulating the PKC

pathway may be relevant in glaucoma as PKC inhibitors relax the trabecular meshwork and affect matrix metalloproteinase and PGF2 alpha.[328] It has been shown that retinal vascular dysfunction due to hyperglycemia was prevented by vitamin E.[329] It has also been reported that vitamin E as d-alpha tocopheryl acetate in 300 to 600 mg/day dosages improved blood flow and reduced visual field change in glaucomatous eyes.[330]

Alpha-tocopherol at 400 to 800 IU per day is an effective antioxidant with fame in reducing the oxidation of low-density lipoproteins to prevent formation of foam cells and thus atherosclerotic plaques. Most interest in vitamin E surrounds the cardiovascular issue. While the studies are variable most point to the fact that vitamin E consumption is associated with some degree of risk reduction in cardiovascular disease with up to 90% of Americans not consuming the RDA of 15 mg/day. [331-334] Results of trials of intervention with vitamin E in vascular disease have been totally non-definitive. [335-337]

In the framework of diabetes, the studies are likewise inconsistent and contradictory.[338-340] One study does however state that oral vitamin E treatment appears to be effective in normalizing retinal hemodynamic abnormalities and improving renal function in type 1 diabetic patients of short disease duration without inducing a significant change in glycemic control. This suggests that vitamin E supplementation may provide an additional benefit in reducing the risks for developing diabetic retinopathy or nephropathy.[341]

Data from the NHANES 1999-2000 indicate that mean dietary intake of alpha-tocopherol is 6.3 mg/day and 7.8 mg/day for women and men, respectively.[342-342] These intakes are well below the current intake recommendations of 15 mg/day. As previously stated it is estimated that more than 90% of Americans do not meet daily dietary recommendations for vitamin E.[344]

Alpha-tocopherol has been shown to enhance the immune system. Additionally, it works synergistically with Omega 3 Fatty Acids to protect cells from tumor necrosis factor alpha (TNF-a) induced apoptosis. Supplementation with Vitamin E has also been shown to increase B cell activity in the aging patient. [345-346] Vitamin E also works synergistically with Vitamin C to reduce inflammatory prostaglandins and increase T cells, IL-2 and tumor necrosis factor beta (TNF-B).

In a prospective observational data from a large cohort of female health professionals, higher dietary intakes of lutein/zeaxanthin and vitamin E from food and supplements were associated with significantly decreased risks of cataract. [347] Of interest, a recent study points to the fact that results demonstrated that there was no significant difference between the 600 mg vitamin E and placebo groups in the incidence of cataract when vitamin E was the only intervention.[348] While this might surprise some, nutrition and health are a combination of many elements. In the realm of ARMD, one study showed evidence that antioxidant (beta-carotene, vitamin C, and vitamin E) and zinc supplementation slowed down the progression to advanced AMD and visual acuity loss in people with signs of the disease, but no evidence that vitamin E or beta-carotene prevented AMD. [349-351] Health is not a single item but rather a cornucopia of actions and these two contradictory studies point to that.

Upper levels for safety of consumption of vitamin E are established by the Food and Nutrition Board of the Institute of Medicine to minimize hemorrahage for alpha-tocopherol supplements are 1,000 mg/day of alpha-tocopherol in any form (equivalent to 1,500 IU/day of RRR-alpha-tocopherol or 1,100 IU/day of all-rac-alpha-tocopherol). One meta-analysis reported that to reduce the risk of any disease that 2000 IU/day were necessary to reduce the risk by 6%.[352] Other studies found no evidence of the decrease of the risk of death with vitamin E supplementation.[353-355]

Drug interactions must be taken into account realizing that hemorrhage at excessive dosages is a potential issue. Any pharmaceutical agents, foods or supplements such as gingko biloba should raise the caution of interaction.

Scientists at the Linus Pauling Institute in Oregon feel there exists credible evidence that taking a supplement of 200 IU (134 mg) of natural source d-alpha-tocopherol

(RRR-alpha-tocopherol) daily with a meal may help protect adults from chronic diseases, such as heart disease, stroke, neurodegenerative diseases, and some types of cancer. The amount of alpha-tocopherol required for such beneficial effects appears to be much greater than that which could be achieved through diet alone. ((lpi.oregonstate.edu) Controversy reigns with recommendations on Vitamin E and any dosages beyond RDA should be carefully considered in view of other health and nutritional issues.

Natural sources of alpha-tocopherol include olive oil, sunflower oil, nuts, whole grains , green leafy vegetables but usually provide less than the RDA of 15 mg/day of RRR-alpha-tocopherol.[356] Supplements made from entirely natural sources contain only RRR-alpha-tocopherol (also labeled d-alpha-tocopherol). RRR-alpha-tocopherol is the isomer preferred for use by the body, making it the most bioavailable form of alpha-tocopherol. Synthetic alpha-tocopherol is less bioavailable and only half as potent. The formulas for conversion to the RRR form are:

- RRR-alpha-tocopherol (natural or d-alpha-tocopherol):
- IU x 0.67 = mg RRR-alpha-tocopherol
- all-rac-alpha-tocopherol (synthetic or dl-alpha-tocopherol):
- IU x 0.45 = mg RRR-alpha-tocopherol.

Lutein/Zeaxanthin

The yellow color of the macula lutea is due to the presence of the carotenoid pigments lutein and zeaxanthin. In contrast to human blood and tissues, no other major carotenoids including Beta-carotene or lycopene are found in this tissue.[357] The associations between MP density and serum lutein, serum zeaxanthin, and adipose lutein concentrations are stronger in men than in women.[358]

A number of studies intended to examine trends in a population suggest a link between increased lutein and decreased risk of eye disease:

In 1994, a National Eye Institute (NEI)-supported study indicated that consumption of foods rich in carotenoids — particularly green, leafy vegetables such as collard greens, kale, and spinach — was associated with a reduced risk of developing macular degeneration.[359]

In 1999, data from the Nurses Health Study showed a reduced likelihood of cataract surgery with increasing intakes of lutein and another carotenoid — zeaxanthin. [360]

In 1999, the Health Professionals Follow-up Study found a trend toward a lower risk of cataract extraction with higher intakes of lutein and zeaxanthin. [361]

In 1999, a follow-up to an NEI-supported population-based study — called the Beaver Dam Study — concluded that people with diets higher in lutein and zeaxanthin had a lower risk of developing cataract. [362]

In 2001, data from the Third National Health and Nutrition Examination Survey reported that higher intakes of lutein and zeaxanthin among people ages 40-59 may be associated with a reduced risk of advanced AMD. [363]

Conversely, in 1998, the Beaver Dam Study found no significant association between the risk of either early or advanced AMD in groups that had either the highest intakes of lutein and zeaxanthin or the lowest intakes of lutein and zeaxanthin. The study researchers caution that generally, the consumption of lutein and zeaxanthin in this population may have been too low to have had an impact on the risk of AMD. [364-365]

In the 2004 LAST (Lutein Antioxidant Supplement Trial) study, 90 AMD patients were supplemented daily with an OcuPower supplement capsule containing 10 mg of crystalline FloraGLO lutein, 10 mg lutein plus a mixed antioxidant formula, or placebo for 12 months. The average American ingests one to two mg of lutein daily. Patients ingesting the lutein supplement experienced significant improvements in several objective measurements of visual function including glare recovery, contrast sensitivity, and visual acuity vs. placebo. Patients also experienced a 50% increase in macular pigment density relative to those on placebo.[366]

In the 2007 LAST study it was found that individuals with the lowest Macular Pigment Optical Density (MPOD) and in greatest need of supplementation, were also likely to benefit from lutein or the lutein plus antioxidant.[367]

Another study evaluated a total of 1802 women from ages 50 to 79. These women were described as having dietary and serum levels of lutein and zeaxanthin either above the 78th (high) or below the 28th

(low) percentile. The prevalence of nuclear cataract was 23% lower in the high-diet group compared with the low-diet group. Furthermore, those in the highest quintile were 32% less likely to have a nuclear cataract compared with the lowest quintile. [368]

Higher dietary intake of lutein/zeaxanthin was independently associated with decreased likelihood of having neovascular AMD, geographic atrophy, and large or extensive intermediate drusen.[369-370] In non-advanced AMD eyes, a selective dysfunction in the central retina (0 degrees – 5 degrees) can be improved by the supplementation with carotenoids and antioxidants. No functional changes are present in the more peripheral (5 degrees – 20 degrees) retinal areas.[371] It has been shown that the synergistic action of zeaxanthin and vitamin E or C found in one study demonstrates the importance of the antioxidant interaction in efficient protection of cell membranes against oxidative damage induced by photosensitized reactions.[372]

One report suggests that lutein and zeaxanthin (the only carotenoids found in the lens) may retard aging of the lens.[373] Another reports that observations indicate dietary modulation of diabetic retinopathy risk may be possible by increasing intakes of lutein and lycopene-rich foods.[374] While the studies continue to be both prolific and very controversial very interesting conclusions have been drawn in juxtaposition. On the basis of one evidence-based review, the FDA concluded that no credible evidence exists for a health claim about the intake of lutein or zeaxanthin (or both) and the risk of age-related macular degeneration or cataracts.[375] Another study states that a higher dietary intake of lutein/zeaxanthin was independently associated with decreased likelihood of having neovascular AMD, geographic atrophy, and large or extensive intermediate drusen.[376] A contrary study found only alpha-tocopherol and beta-cryptoxanthin were related to late AMD as single antioxidants. On the other hand, the carotene and carotenoid families as a combination of antioxidants were protectively associated with late AMD. No relationship was found between serum antioxidants and early AMD. Our findings support the hypothesis that a combination of serum antioxidants obtained from the traditional Japanese diet is protective for late AMD, but not for early AMD.[377] Further controversy continues with finding stating that persons with intermediate age-related macular degeneration or advanced age-related macular degeneration (neovascular or central geographic atrophy) in one eye should consider taking the AREDS-type supplements. Further evaluation of nutritional factors, specifically, lutein/zeaxanthin and omega-3 fatty acids will be tested in a multicenter controlled, randomized trial — the Age-Related Eye Disease Study 2 (AREDS2).[378]

No one can even accurately estimate the RDA of Lutein. One study cites the fact that macular concentration of lutein and zeaxantin decreases with age, what exacerbates harmful effect of blue light on photoreceptors. Lutein and zeaxantin act as a filter of the high energy blue light. Besides, these carotenoids are strong antioxidants and neutralize light-generated free radicals. Plant foods are the exclusive dietary sources of the carotenoids. Their average intake in the European countries is several times lower than 6 mg daily, which is the estimated recommended intake.[379] One study is bold enough to say that elderly human subjects with and without AMD can safely take supplements of lutein up to 10 mg/d for 6 months with no apparent toxicity or side effects.[380]

One study covers the ground pretty well stating that observational and clinical trials support the safety of higher intakes of the phytochemicals lutein and zeaxanthin and their association with reducing risks of cataracts in healthy postmenopausal women and improving clinical features of AMD in patients. Additional phytochemicals of emerging interest, like green tea catechins, anthocyanins, resveratrol, and Ginkgo biloba, shown to ameliorate ocular oxidative stress, deserve more attention in future clinical trials. Obtuse, yet obtuse.[381] Yet another spin, The carotenoid zeaxanthin accumulates in the human macula lutea and protects retinal cells from blue light damage.

Thus, consumption of zeaxanthin-rich potatoes significantly increases chylomicron zeaxanthin concentrations suggesting that potentially such potatoes could be used as an important dietary source of

zeaxanthin.[382] Another study chimes in with the assessment that after multivariate adjustment for potential confounders 1980 energy-adjusted intakes of alpha-carotene, beta-carotene, lycopene, total retinol, total vitamin A, and total vitamin E were significantly inversely related to the prevalence of pigmentary abnormalities (PA). Furthermore, increasing frequency of consuming foods high in alpha-or beta-carotene was associated with lower odds of Pigmentary Abnormalities. Alluding to the impact of multiple antioxidants on ARMD.[383]

Another interesting historical twist has presented in the nutritional arena as related to lutein. One report states that concentrations of serum lutein 26% and zeaxanthin 38% increased after 5-wk of 1 egg/d compared with the phase prior to consuming eggs. Serum concentrations of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were not affected. These findings indicate that in older adults, 5 wk of consuming 1 egg/d significantly increases serum lutein and zeaxanthin concentrations without elevating serum lipids and lipoprotein cholesterol concentrations.[384] Another report goes on to say for these reasons, dietary recommendations aimed at restricting egg consumption should not be generalized to include all individuals (70% of the population experiences a mild increase or no alterations in plasma cholesterol concentrations when challenged with high amounts of dietary cholesterol (hyporesponders). It appears that diverse healthy populations experience no risk in developing coronary heart disease by increasing their intake of cholesterol but, in contrast, they may have multiple beneficial effects by the inclusion of eggs in their regular diet.[385] In regard to the potential negative cardiovascular risk other studies suggest as well a potential contribution of lutein and zeaxanthin to the prevention of heart disease and stroke. It is worth noting that recommendations to consume foods rich in xanthophylls are consistent with current dietary guidelines. Lutein and zeaxanthin are xanthophyll carotenoids found particularly in dark-green leafy vegetables and in egg yolks. They are widely distributed in tissues and are the principal carotenoids in most tissue throughout the body.[386-387] In conclusion, the lutein bioavailability from egg is higher than that from other sources such as lutein, lutein ester supplements, and spinach.[388]

The most provocative information to come along in a while is the relationship of Omega 3 fatty acids to the entire process of macular degeneration, ocular disease and systemic disorders. While these are not covered in detail here, it is important to understand the concept of inflammation and how it contributes to ARMD and ocular disorders. One study's objective was to determine the effects of lutein (12 mg/d) and DHA (800 mg/d) on their serum concentrations and macular pigment optical density (MPOD) Lutein supplementation increased MPOD eccentrically. DHA resulted in central increases. These results may be due to changes in lipoproteins. Lutein and DHA may aid in prevention of age-related macular degeneration.[389] Another study corroborates the fact that n-3 Fatty acids, particularly docosahexaenoic acid (DHA), are highly concentrated in brain and retinal tissue and may prevent or delay the progression of dementia and AMD. Low dietary intakes and plasma concentrations have been reported to be associated with dementia, cognitive decline, and AMD risk. They go on to reports that their own unpublished observations from the Framingham Heart Study suggest that > or =180 mg/d of dietary DHA (approximately 2.7 fish servings/wk) is associated with an approximately 50% reduction in dementia risk. At least this amount of DHA is generally found in one commercially available 1-g fish oil capsule given daily.[390] Further information regarding inflammation and AMD demonstrated that Linolenic acid was positively associated with risk of AMD docosahexaenoic acid (DHA) had a modest inverse relation with AMD and that >4 servings of fish/wk was associated with a 35% lower risk of AMD compared with < or = 3 servings/mo. Also total fat intake was positively associated with risk of AMD. The conclusion was a high intake of fish may reduce the risk of AMD.[391] Likewise higher levels of serum antioxidants vitamin C and lutein/zeaxanthin and higher fish intake were associated with lower serum C-Reactive Protein (CRP) levels, whereas serum vitamin E, smoking, and increased body mass index

were associated with increased CRP. Furthermore, serum vitamin E, serum alpha-carotene, and dietary intake of antioxidants and vitamin B6 were associated with lower levels of plasma HCY, whereas hypertension was associated with increased HCY. C-reactive protein and HCY levels are related to traditional dietary and behavioral factors associated with age-related macular degeneration. [392] One more study corroborates the relationship stating that a higher frequency of fish consumption was associated with decreased odds of late ARM. Subjects with higher energy-adjusted intakes of cholesterol were significantly more likely to have late ARM. The amount and type of dietary fat intake may be associated with ARM.[393]

With review of the issues of lutein, ambiguity reigns. One report advocates that vitamins C and E, and lutein/zeaxanthin should be included in our theoretically ideal ocular nutritional supplement.[394] Another understates saying that until scientifically sound knowledge is available we recommend for patients judged to be at risk for AMD to: alter their diet to more dark green leafy vegetables, wear UV protective lenses and a hat when outdoors. [395] Lutein and zeaxanthin do not exist in a vacuum and the entire issue of health is multifactorial. Diet looms as critically important in the genesis of all disease and AMD is not an exception. An illustration of that is the fact that high consumption of corn bread indicated significant association with central vision loss (OR 0.4; 95% CI 0.2, 0.9)in 168 rural elders.[396] This relates to the fact that cross-sectional studies indicate that diets that provide a higher dietary glycemic index (dGI) are associated with a greater risk of age-related macular degeneration (AMD). Persons at risk of AMD progression, especially those at high risk of advanced AMD, may benefit from consuming a smaller amount of refined carbohydrates.[397] The association between dietary glycemic index (dGI) and AMD from the AREDS cross-sectional analysis at baseline suggests that a reduction in the dGI, a modifiable risk factor, may provide a means of diminishing the risk of AMD.[398]

While Lutein and Zeaxanthin are readily available in dark leafy green vegetables, patients with concerns about blood clotting must avoid some of these because of the Vitamin K-clotting factor-in these vegetables. Lutein and Zeaxanthin may be supplemented in pill or egg form without fear of interference with blood thinners.

Glutathione

Glutathione is the most abundant antioxidant in the body, produced in the body, found in every cell in the body and is the primary free radical fighter. It is the regenerator of immune cells. It is produced in every cell with the help of selenium, magnesium and vitamin C. Glutathione production decreases with age. The pathway for collagen remodeling and apoptosis induction in glaucoma seems to be exogenously influenced by water-soluble antioxidants, for example, glutathione. The pathway for elastin remodelling and apoptosis induction seems to be influenced by endogenous lipid-soluble antioxidants, for example, vitamin E.[399] Supplementation with glutathione is not accomplished well orally and the utilization of supplementation is not well documented.

Magnesium

Magnesium is a mineral and is very short acting. The majority of magnesium is within the skeleton, with about 25% in muscle and it is involved in more than 300 essential reactions within the body.[400] Magnesium is involved in glutathione production, cell membrane genesis and chromosome activity. As related to cellular mechanism magnesium is critical in ions transport across cell membranes, as evident in the neurodegeneration model. Magnesium acts as a smooth muscle relaxant, partially inhibits the effect of endothelin (a vasoconstrictor), and is a calcium channel blocker, and as such often acts as a vasodilator and improves peripheral circulation.[401-404] Some studies suggest that magnesium plays a role in hypertension and cardiovascular disease but there is no definitive work to underscore the recommendations for intervention.[405-411] Magnesium is very involved in the ATP-synthesizing protein in mitiochondria and as such in the neuroprotection pathway. [412]

Magnesium seems to have a beneficial effect on the visual field in glaucoma patients with both increased and normal IOP — possibly by alleviating vasospasm at 300 mg/day. Magnesium also works to activate enzymatic

systems.[413-414] Magnesium does not directly influence immune function but rather is critical in 300 enzymatic functions in the body. Magnesium deficiency causes an increase in pro-inflammatory cytokines and an excess production of free radicals and as a result increases the effects of the inflammatory process.

Magnesium depletion is commonly associated with both insulin dependent (IDDM) and non-insulin dependent (NIDDM)diabetes mellitus. Between 25% and 38% of diabetics have been found to have decreased serum levels of magnesium (hypomagnesemia) perhaps associated with urinary issues.[415] It is suggested but not proven that magnesium supplementation may be beneficial in patients with diabetes.[416-417]

From a neurological standpoint, persons with recurrent migraines have lower magnesium levels.[418] Supplementation to alleviate the headaches has produced conflicting results and the levels of supplementation to achieve modulation of the headaches result in side effects.[419-420]

Magnesium absorption is impaired by a low protein diet, a high fiber diet, and excesses in zinc consumption, GI disorders, bariatric surgery renal disorders, chronic alcoholism, increasing age.[421] Magnesium can interact with digoxin, anti-malarials, some drugs to treat osteoporosis,, tranquilizers, oral anticoagulants and some antibiotics. In seriously ill patients, the primary care physician should be consulted.

Consumption of magnesium in the US is considered lower than the RDA. Natural sources of magnesium are cereals, brown rice, nuts, beans, spinach, chard, okra and bananas. Recommended daily dosage is 420 mg/day for men over 30 and 320 mg/day for women over 30 years of age. The recommended supplement is 100 mg/day assuming some dietary consumption of magnesium. The tolerable upper level of intake (UL), which is 350 mg/day set by the Food and Nutrition Board.[422]

Zinc

Zinc is an essential trace element for the proper functioning of a number of human systems. Zinc is critical for 100 different enzymes relevant to their catalytic role.[423] Zinc is also critical in the structure of proteins and cell membranes. Cell membranes are susceptible to oxidative damage with loss of zinc. [424] Zinc also has a role in gene expression acting in the role of transcription factors as well as having responsibilities in cell signaling. Zinc also plays a role in apoptosis.[425]

Zinc served the role as the entry point for eye care into the realization of the importance of nutrition in ocular health. Use in the management of macular degeneration has resulted in mixed reports. [426-432] The element is, however, a part of the AREDS recommendation. When speaking about commercially available vitamin supplements it should be noted that zinc at 80 mg/day resulted in increase genitourinary hospital admissions in the AREDS study.[433] It has also been found that based on the evidence it is suggest that zinc plays a role in sub-RPE deposit formation in the aging human eye and possibly also in the development and/or progression of AMD. [434]

Large quantities of zinc interfere with copper bioavailability by inducing intestinal sysnthesis of metallothionein, which traps copper.[435] This action may then lead to cupric anemia. Zinc consumption must be accompanied by copper supplementation. Iron supplementation and calcium combined with phytic acid (limes) may also decrease the availability of zinc.[436] Zinc is required for the enzyme that converts retinol (vitamin A) to retinal. Zinc deficiency is associated with decreased release of vitamin A from the liver, which may contribute to symptoms of night blindness that are seen with zinc deficiency.[437] High doses of zinc also impact negatively in the absorption of magnesium.[438]

Zinc is important in the immune system and has gained much press in regard to the prevention of colds and respiratory disease and gastrointestinal disorders especially as related to children.[439-443] There are also implications regarding diarrhea with The World Health Organization and the United Nations Children's Fund currently recommending zinc supplementation as part of the treatment for diarrheal diseases in young children.[444] A recent meta-analysis of published randomized controlled trials on the use of zinc gluconate lozenges in colds found that evidence for their effectiveness in reducing the duration of common colds was still lacking.[445] Use of intranasal zinc is also of questionable value.[446-447] with recent

removal from the market for loss of smell.[448]

Zinc picolinate has been promoted as a more absorbable form of zinc, but there are few data to support this idea in humans. In order to prevent copper deficiency, the U.S. Food and Nutrition Board set the tolerable upper level of intake (UL) for adults at 40 mg/day, including dietary and supplemental zinc.[449] Most AREDs formulas contain double that recommendation. The recommendation for zinc is to take a multivitamin supplement containing 100% of the daily values (DV) of most nutrients will generally provide 15 mg/day of zinc. Use of zinc may decrease the absorption of tetracyclines and quinolones so an interval of two hours is appropriate.[450]

Natural sources of zinc include crab, oysters, beef, pork, dark meat chicken and turkey, yogurt, cheese, milk, cashews, almonds, peanuts, and beans.

Zinc is critical in a number of different interactions in the body but in excess there may be danger both systemically and in the potentiation of ARMD.

Part 4 of this series will be a continuation of the discussion of the specific supplements and their benefits in the management of diseases and disorders. This will include an extensive discussion of the very timely issue of Omega 3 and Omega 6 fatty acids. It will be printed in Spring, 2010.

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